# Economic Evaluation in the Context of Multimorbidity: A Systematic Review and Cost-Consequence Analysis

**by**

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# Abstract

Multimorbidity—the co-occurrence of two or more chronic diseases, where one condition is not necessarily more important than the other(s)—is a significant global healthcare issue. This thesis examines interventions for multimorbidity in the context of economic evaluation and comprises (i) a systematic review assessing the cost-effectiveness of interventions targeted to people with multimorbidity and (ii) a cost-consequence analysis, performed alongside a randomized controlled trial, comparing an interactive digital health-based self-management program for people with multimorbidity with usual care. The review, consisting of 17 economic evaluations, highlighted variation in the methods used to assess cost-effectiveness, including the choice of study design and the valuation of outcomes. Overall, a finding from the review was that interventions with self-management components were often shown to be cost saving, a conclusion that was also supported in the trial-based cost-consequence analysis (albeit with the caveat that some key resources were not costed in the analysis).



**Keywords**: cost-consequence analysis; cost-effectiveness; economic evaluation; multimorbidity; multiple chronic diseases; systematic review

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# List of Acronyms

| | |
|---|---|
| AQoL-4D | Assessment of Quality of Life four-dimension questionnaire |
| BC | British Columbia |
| CAD | Canadian dollar |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CBA | Cost-benefit analysis |
| CCA | Cost-consequence analysis |
| CCEMG | Campbell and Cochrane Economics Methods Group |
| CEA | Cost-effectiveness analysis |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CKD | Chronic kidney disease |
| CIHI | Canadian Institute on Health Information |
| CINAHL Complete | Cumulative Index to Nursing and Allied Health Literature Complete |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CES-D | Centre for Epidemiologic Studies Depression scale |
| CMA | Cost-minimization analysis |
| COPD | Chronic obstructive pulmonary disease |
| CUA | Cost-utility analysis |
| DALY | Disability-adjusted life year |
| DARE | Database of Abstracts of Reviews of Effects |
| DHI | Digital health intervention |
| ED | Emergency department |
| eHEALS | eHealth Literacy Scale |
| ePRO | Electronic patient-reported outcome |
| EMBASE | Excerpta Medica Database |
| FDA | Food and Drug Administration |
| GBP | Great British pound |
| GDP | Gross domestic product |
| heiQ | Health Education Impact Questionnaire |
| HF | Heart failure |
| HRQoL | Health-related quality of life |
| HTA | Health Technology Assessment |
| IHD | Ischemic heart disease |

| | |
|---|---|
| MCS | Mental component summary |
| MeSH | Medical Subject Headings |
| MID | Minimally Important Difference |
| MOS | Medical Outcomes Study |
| MSP | Medical Services Plan |
| NA | Not applicable |
| NICE | National Institute for Health and Care Excellence |
| NHS | National Health Service |
| NHS EED | NHS Economic Evaluation Database |
| PCS | Physical component summary |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QHES | Quality of health economic studies |
| QALY | Quality-adjusted life year |
| SF-36 | 36-item Short Form survey |
| SFU | Simon Fraser University |
| SMS | Short message service |
| ICER | Incremental cost-effectiveness ratio |
| iCDM | Internet chronic disease management |
| RCT | Randomized controlled trial |
| UK | United Kingdom |
| US | United States |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |
| WTP | Willingness-to-pay |

# Chapter 1.

# Introduction

## 1.1. The global burden and challenges with multimorbidity

There are different definitions of multimorbidity in the literature. Statistics Canada defines multimorbidity as "*having three or more of the selected chronic conditions: arthritis, high blood pressure, diabetes, cancer (ever diagnosed), heart disease (ever diagnosed), stroke, mood disorders and anxiety",*[1] whereas the National Institute for Health and Care Excellence (NICE), an organization that provides evidence-based guidelines and recommendations for health and care in England and Wales, defines multimorbidity as the *"presence of two or more long-term health conditions".*[2] Neither of these definitions are used to define multimorbidity in this thesis. Instead, I adopt the definition of Boyd and colleagues, who define multimorbidity as, "the co-existence of two or more chronic conditions, where one is not necessarily more central than the others".[3] The definition of Statistics Canada was not chosen given the fact that having three or more chronic conditions is often referred as "complex multimorbidity" in the literature.[4–6] While NICE's definition is the most widely cited definition of multimorbidity,[4] it was not selected because it is inclusive of patients with an index condition (i.e., the primary medical condition or disease that is being considered or studied).[7] This means NICE's definition is inclusive of comorbidity — where comorbidity refers to any separate additional condition that either currently exists or may arise alongside the index disease being investigated during a patient's clinical journey.[8] The reason why Boyd and colleagues' definition[3] is most appropriate for this thesis is that unlike the Statistics Canada definition,[1] which specifies having three or more chronic conditions, it allows for the inclusion of individuals with two or more chronic conditions. This broader scope (not just complex cases) better captures the diverse range of multimorbid presentations and ensures that no individuals are excluded from the study based on arbitrary cutoffs. Boyd and colleagues' definition also emphasizes the co-existence of chronic conditions, without prioritizing one as the main condition (index condition).[3] Since this thesis

differentiates between multimorbidity and comorbidity, focusing on the co-existence of multiple conditions (without an index condition) is a better fit for the research questions.

Multimorbidity has also emerged as a substantial global healthcare issue. The number of people with multimorbidity is increasing worldwide.[9] In the United States (US), the estimated occurrence of multimorbidity rose from 21.8% in 2001 to 26.0% in 2010.[10] In Europe, the prevalence of multimorbidity in 2015 varied between 32.1% in Switzerland to 53.3% in Estonia.[11] Multimorbidity can impact individuals of all age groups, although its burden is particularly pronounced among older adults with 2021 estimates suggesting that over 50% of the global adult population aged 60 years and above are affected by multimorbidity.[9] Multimorbidity is significantly associated with a higher risk of mortality, diminished quality of life, impaired functional health status, and decreased physical functioning.[12,13] People living with multimorbidity exhibit increased use of healthcare resources compared with people with one chronic disease. For example, in a retrospective cohort study, Salisbury et al. reported that 58% of the cohort with multimorbidity accounted for 78% of the total primary care consultations.[14]

While the global burden of multimorbidity presents challenges for practitioners, decision-makers and patients, a further important consideration is its definition (and, therefore, all aforementioned statistics should be interpreted in the context of the respective definitions). For more than two decades, Van Den Akker et al. have advocated for clearly distinguishing between the terms ‘comorbidity’ and ‘multimorbidity’.[15] Earlier in the introduction, the term ‘comorbidity’ was defined by using a definition which was introduced by the clinician and researcher Alvan Feinstein in 1970, referring to any separate additional condition that either currently exists or may arise alongside the primary disease being investigated during a patient's clinical journey.[8] From around 1976, there was a rising trend to utilize the term ‘multimorbidity’ when referring to patients with multiple chronic conditions.[16] In response to the growing ambiguity surrounding the two terms, Van Den Akker et al.[15] suggested that comorbidity should align with Feinstein's original definition, while multimorbidity should be defined as the simultaneous presence of multiple chronic diseases within an individual. However, despite this suggestion, the terms have continued to be used somewhat interchangeably in the peer-reviewed health science literature.[17] Notably, in 2018, the Medical Subject Headings (MeSH) for multimorbidity and comorbidity were separated.[18]

The distinction of whether a person has an index disease may appear insignificant, but it holds significance as it mirrors how various parts of the health system perceive and engage with people who have multiple chronic conditions.[16] While the concept of comorbidity is relevant in specialized care settings that revolve around specific diseases, its disease-centric focus solidifies health systems' single disease, siloed structure.[16] This structure could cause fragmented care for patients with two or more chronic conditions where one is not more important than the other(s) as different parts of the health system may view the disease they are managing as the primary condition.[16] For example, in a 2023 cohort study comprising 4.7 million Danish adults, high levels of fragmented care among patients with multimorbidity were associated with both a higher use of potentially harmful medications and a higher risk of death, even after adjusting for demographics, socioeconomic factors, and underlying conditions.[19] In a 2023 observational cross-sectional study of older adults with multimorbidity, the fragmentation of care was associated not only with a higher number of prescribed drugs, but also with higher medical costs, even when older adults had the same number of chronic diseases.[20] Several qualitative studies have also indicated that emphasis on a single disease is not satisfactory for patients with multimorbidity and their healthcare providers because of a limited consultation time with a physician and a lack of care coordination between primary and secondary care.[21–23] Not focusing on a single condition could be a more efficient way to manage patients with multimorbidity because the focus will be on the patient as a whole, giving them holistic care, where their symptoms, preferences, and priorities, are the main focus, with no disease being prioritized over any other.[16] However, it is important to acknowledge that managing multimorbid patients through this 'multimorbidity lens' rather than 'comorbidity lens' would not necessarily reduce the harms associated with fragmentation of care. There is currently a paucity of research studies on the most effective strategies for delivering holistic care to patients with multimorbidity, beyond simply avoiding a comorbidity-based approach.

One of the most difficult challenges for healthcare systems, clinicians, and researchers is designing and delivering interventions which improve outcomes for patients with multimorbidity.[16] This is because multimorbidity-focused interventions need to adopt a more generic focus that works across a broad range of conditions, which ultimately makes outcomes difficult to identify.[24] Comorbidity-focused interventions on the other hand aim to address specific conditions occurring together and assess outcomes related

to those particular diseases. Usual management of multimorbidity relying on a single-disease paradigm instead of recognizing the complexity of having multimorbidity is considered obsolete, and there are considerations about taking a different approach to addressing multimorbidity.[25,26] Patient self-management is identified as a possible innovative way to tackle multimorbidity. Healthcare systems are shifting toward patient-centred care, and to be successful in it, patients must engage in self-management.[27] Medication management, keeping consistency in healthy lifestyle behaviours, and self-monitoring of symptoms are key ingredients of successful patient self-management.[28] Different types of digital technologies can support patient self-management with short message service (SMS), mobile app, telephone, video conferencing system, telemonitoring, teleconsultations, and wearable medical device.[27,29]

## 1.2. Digital health interventions for multimorbidity

In recent years, there has been growing recognition of the valuable role that digital health interventions (DHIs) in particular could play in integrating and enhancing care for patients with multimorbidity.[30] Chapter 3 will indeed focus on a particular DHI designed for patients with multimorbidity. The absence of agreement on the definition of digital health has resulted in ambiguity and uncertainty among academics, policymakers, healthcare providers, and consumers. The international call for definitions of digital health in 2001 failed to elicit published responses, leading to an updated call in 2004, underscoring the persistent ambiguity and uncertainty surrounding the concept. Indeed, Pagliari and colleagues conducted a qualitative study which identified 36 distinct definitions of digital health.[31] The World Health Organization (WHO) views digital health as "*the field of knowledge and practice associated with the development and use of digital technologies to improve health*".[32] According to the WHO, digital health involves several areas that are widely recognized as being part of or related to it, including artificial intelligence, big data, blockchain, health data, health information systems, the infodemic, the Internet of Things, interoperability, and telemedicine. As per the US Food and Drug Administration (FDA), the term digital health encompasses mobile health, telemedicine, telehealth, wearable devices, and personalized medicine.[29] There is one

systematic review that sought to determine the effectiveness of any kind of DHIs created to improve outcomes in people with multimorbidity.[33] Six studies were identified and multimorbid diseases were limited to a few specific conditions, such as diabetes, hypertension, and chronic obstructive pulmonary disease (COPD), leaving a significant gap in evidence for patients with other coexisting conditions. The results showed that DHIs identified in the studies demonstrated moderate evidence of enhancing disease control measures, but there is limited evidence and no demonstrated benefits on overall health status. The findings also indicate that current evidence for the use of DHIs is limited and that these treatments have rarely been evaluated systematically. The authors also stressed the importance of evaluating the cost-effectiveness of DHIs for people with multimorbidity.

## 1.3. Economic evaluation in healthcare decision-making

Healthcare resources such as physicians, hospitals, and surgery equipment are scarce in Canada and other countries. Therefore, decisions must be made regarding deploying these limited healthcare resources.[34] People who make these decisions often face situations where they need to evaluate between two or more alternative policies, services, or interventions, intended to improve health. Choosing one course of action over another needs to be made by considering the costs and benefits of each one, and this type of evaluation is often referred to, broadly, as economic evaluation.

According to the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine, costs associated with an intervention can be categorized into three groups: (i) formal healthcare sector costs (medical costs), including future related and unrelated medical costs paid by third-party payers or out-of-pocket by patients themselves; (ii) informal costs, such as unpaid caregiver time and patient time; and (iii) non-healthcare costs, such as cost of social services and productivity losses.[35] The Canadian Agency for Drugs and Technologies in Health (CADTH),[36] which is a health technology assessment agency in Canada, specifies that the costs to be included in an economic evaluation should adhere to the chosen perspective, where ‘perspective’

refers to the viewpoint chosen when determining which outcomes and costs are relevant for inclusion.[37] A key role of CADTH is to provide evidence-based information and recommendations to help healthcare decision-makers, such as clinicians, policymakers, and healthcare organizations, make informed decisions about the use of healthcare technologies. In accordance with CADTH, costs should be analyzed from the publicly funded healthcare payer perspective. Based on the "*Perspective and Costing in Cost-Effectiveness Analysis*" paper written by Kim et al.,[38] study perspectives can be categorized in the following ways: healthcare payer (costs incurred by healthcare payer), healthcare sector (similar to the healthcare payer perspective but accounts for all costs of healthcare, regardless of who bears the cost), limited societal (costs beyond those captured by the healthcare sector perspective, such as patient time, patient transportation, productivity loss, and unpaid caregiver time), and societal perspective (broader than the limited societal perspective, takes into account the overall public interest by including all resources that could be used for other purposes, and considers cost impacts on additional sectors like the environment or education).

Healthcare consequences, benefits, or outcomes (these terms are frequently used interchangeably) are another important aspect of economic evaluation, and they can be seen as benefits or outcomes associated with a healthcare intervention.[39] Some examples of health outcomes used in economic evaluations include, but are not limited to, quality-adjusted life years (QALYs) gained, life-years gained, number of heart attacks avoided, and blood pressure reduction.[40] These health benefits can be drawn from a variety of sources, encompassing both randomized controlled trials (RCTs) and observational datasets.[34] These observational datasets may include registries, administrative databases, clinical case series, and long-term epidemiological studies. Health benefits can be integrated into economic evaluations through three approaches. Firstly, economic evaluations can occur concurrently with a single clinical study, utilizing individual patient-level data. Alternatively, economic evaluations can employ decision analytical modelling. In this scenario, models generally synthesize a compilation of health outcomes data from various clinical studies. Lastly, economic evaluation can use a combination of the two.[34]

## 1.4. Analytic frameworks for economic evaluation

### 1.4.1. Trial-based economic evaluation

The two main analytic frameworks for economic evaluation are trial-based and model-based analyses. Trial-based evaluations use an RCT as the vehicle for conducting an economic evaluation.[41] Since 1994, around 30% of the economic evaluations published in the NHS Economic Evaluation Database (NHS EED) have relied on data derived from a single RCT.[42] Indeed, many funding organizations, such as the United Kingdom (UK) National Institute for Health Research Health Technology Assessment Programme, commonly require that evaluations of cost-effectiveness be integrated into the planning and design of randomized trials.[41] One of the advantages of trial-based economic evaluations is that it is convenient for economists since it gives them an early opportunity to get reliable cost-effectiveness results at a low marginal cost. Another advantage is that the process of randomization guarantees that any known or unknown factors that could introduce bias are evenly distributed among the treatment groups, effectively reducing the potential for bias.[43] Simultaneously, its pragmatic design enhances the applicability of the results to real-world clinical practice. However, it is contended that, in many instances, trial-based studies constitute a partial and constrained form of analysis.[42] First, it fails to make a comparison between all relevant alternatives. Due to the expenses associated with research and the considerations regarding the number of participants, only a few RCTs will encompass more than two alternatives, usually consisting of new technology and a single established ‘standard’ intervention, reflecting usual care. Nevertheless, it is almost always the case that a variety of existing interventions are employed to varying extents in everyday clinical practice. Second, in numerous trial-based economic evaluations, the duration of follow-up in the trial is often shorter than the suitable time horizon required for the economic analysis. While this may not be the situation for trials addressing the treatment of specific acute conditions or alternative management approaches for terminally ill patients, it is commonly observed in trial-based economic evaluations focused on various aspects of healthcare. This gap between the costs and benefits estimated within the trial and those essential for informed decision-making can present a challenge when assessing the long-term

economic impact of healthcare interventions. Another significant criticism of trial-based economic evaluations is the failure to encompass all relevant evidence. Perhaps the most substantial critique in this regard is that a single trial is highly improbable to encompass all the evidence needed for a comprehensive economic evaluation. For instance, there might be a lack of data regarding resource utilization or measurements of health-related quality of life (HRQoL), both of which are crucial for conducting a thorough economic evaluation.

### 1.4.2. Model-based economic evaluation

Decision analytical modelling is another analytical framework that can be adopted for conducting an economic evaluation. Decision analytical modelling involves the comparison of anticipated costs and outcomes associated with various decision options.[41] It achieves this by synthesizing information from various sources and employing mathematical techniques, often facilitated by computer software. These sources could include clinical, resource use, and outcome data collected alongside randomized trials, but are also likely to include evidence from other types of study such as cohort studies and surveys.[34] The primary objective is to furnish decision-makers with the most reliable evidence to aid in making informed decisions, such as whether to adopt a new intervention or not.[41] Trial-based economic evaluations and decision analytical modelling should be viewed as complements rather than substitutes.[42] RCTs give estimates of specific parameters within a particular group of patients in a specific healthcare setting. On the other hand, decision models serve as a framework that allows evidence from various sources to be applied to a particular decision problem for a defined population and context. It is crucial to clarify this distinction between measurement (conducted in trials and other primary studies) and decision-making (which requires an analytical structure to direct evidence toward the specific decision problem at hand). This underscores that models and trials are complementary tools rather than interchangeable substitutes. Both analytic frameworks (trial-based and model-based economic evaluations) can be adopted for different types of economic evaluation, which are described in the following section.

## 1.5. Types of economic evaluation

There are five different types of economic evaluation described in health economics literature: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-consequence analysis (CCA), and cost-minimization analysis (CMA).[44] There are, however, disagreements regarding whether CMA should be considered an economic evaluation.[45,46] One view is that CMA is considered a suitable approach for evaluating interventions when it is already established that the interventions will produce the same benefit.[47] In such cases, the primary emphasis is on examining the costs involved to determine the least costly alternative (because, by definition, this would mean the least costly alternative is a more efficient use of resources). However, Briggs and O'Brien[45] declared "*the death of CMA*" in 2001 and argued that it is not appropriate to conduct this kind of analysis when both data on costs and effects are available. Instead, CEA, CBA, or CUA should be performed since they allow for the comparison of treatments with different effectiveness, regardless of clinical or statistical significance, and such analyses can take into consideration the uncertainty around the effect estimate. The utility of CMA is also restricted due to the challenge of proving that the effectiveness of two or more interventions is equal.[48] Since the outcomes of clinical trials cannot be predicted in advance, it is also not feasible to plan for conducting a CMA alongside an RCT because there is no assurance that the health outcomes being compared will be equivalent.[49] Dakin and Wordsworth explained that CMA is in fact only appropriate if the difference in costs between two treatments is large enough that no plausible difference in benefits could alter the conclusion of the analysis.[46] Considering all the above, CMA is not regarded as an economic evaluation in the remainder of this thesis.

### *Cost-effectiveness analysis*

CEA involves the evaluation of costs and consequences of different treatments by using clinical outcomes in natural units.[50] These natural units can encompass different clinical end points, such as symptom-free days, cases diagnosed, or life-years gained. When conducting CEA, it is essential to focus on comparing the incremental costs and outcomes between the new intervention and usual care. This comparison should highlight the additional expenses introduced by one program in contrast to the extra benefits it provides. This is called the incremental cost-effectiveness ratio (ICER), which

is determined by dividing the difference in costs (the incremental costs) by the difference in effectiveness (the incremental benefits) between the new intervention and usual care. The cost-effectiveness plane is a commonly used method for presenting the incremental results of a CEA (Figure 1).

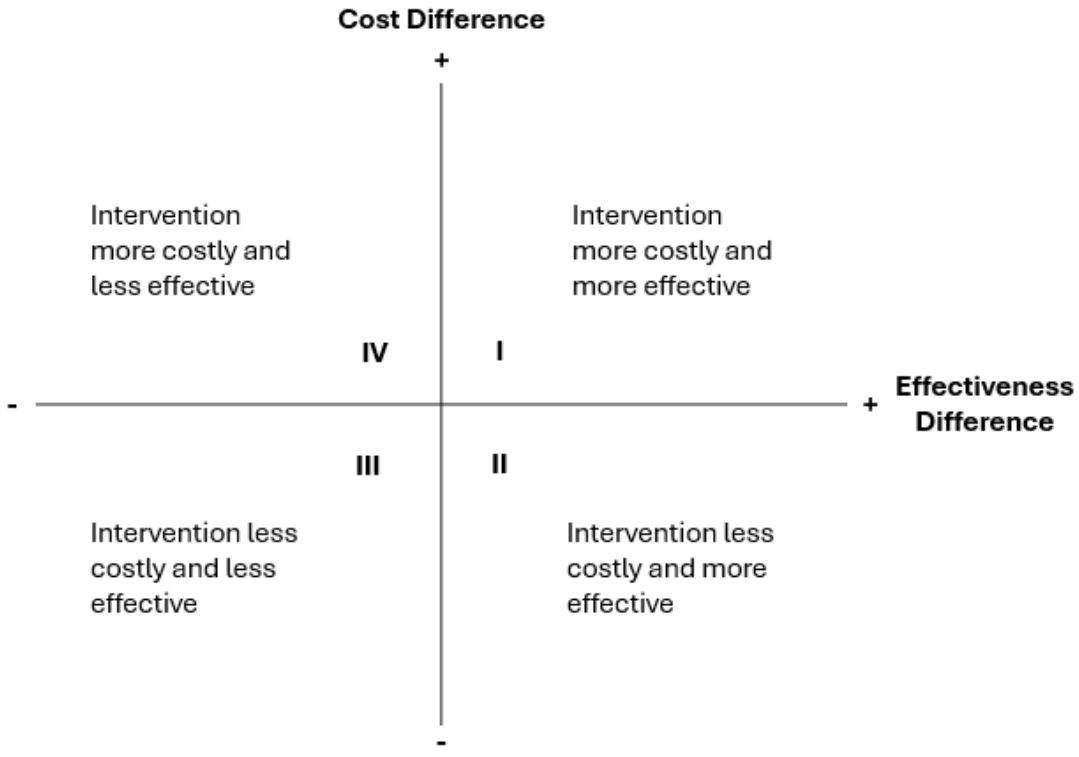


**Figure 1.1: Visual depiction of cost-effectiveness plane[a]**

[a] Incremental results falling into either quadrants II or IV are considered 'dominant' and 'dominated' respectively. Interventions in quadrant I are considered more effective but more costly, and interventions in quadrant III are considered less effective but less costly; ICERs need to be computed and compared in these cases.

In Figure 1.1, incremental results falling into either quadrants II or IV are considered 'dominant' and 'dominated' respectively, and do not require the calculation of ICERs. This is because they are either more effective and less costly (quadrant II) or more expensive and less effective (quadrant IV). Typically, interventions in quadrant II are almost always accepted, while those in quadrant IV are typically rejected. However, for interventions in quadrant I (more effective but more costly) and quadrant III (less effective but less costly), ICERs need to be computed and compared. Once the ICER between two interventions is calculated (i.e., for quadrant I or quadrant III scenarios only), the decision to accept the most cost-effective option often hinges on a maximum

ICER threshold set by policy makers. This willingness-to-pay (WTP) threshold can vary based on healthcare goals and available budgets. A WTP threshold, as defined by the WHO, represents an estimation of what a healthcare consumer would be willing to spend to obtain a particular health benefit.[51] In the US, a WTP threshold ranging from United States Dollar (USD) 50,000 to USD 100,000, which was initially set in 1982, continues to be a point of reference and remains in use by various stakeholders including public and private policymakers, insurers, and researchers today.[52]

There are several advantages of CEA. It demands fewer resources because the health outcome is typically already being assessed as part of the study's effectiveness component.[50] This approach tends to be more straightforward for clinicians to understand because it relies on familiar clinical end points. Nonetheless, the primary drawback of CEA is its limited ability to evaluate the opportunity cost, which refers to the benefits forfeited in other programs funded by the same budget.[34] To make a well-informed decision, decision-makers must compare the advantages of introducing a new intervention with the losses incurred by displacing existing programs. This necessitates the use of a generic measure of benefit that is applicable to all the interventions under the decision-maker's purview. One of the most common generic measures of benefit called QALY is the main component of CUA.

### *Cost-utility analysis*

CUA is often referred to as a variant of CEA, and it is the most common published type of economic evaluation.[34] The primary benefit of CUA over CEA is its capability to compare outcomes across varying disease conditions.[50] This attribute allows for the assessment of the opportunity cost associated with moving limited resources from one healthcare area to another. It is also a type of economic evaluation that primarily centres on measuring a patient's preference for living in a specific health state. This preference outcome is quantified using a health utility score, interpreted on a scale between 1 (representing full health) and 0 (dead). While non-preference-based outcome measures are objective metrics used to assess health status, functioning, or clinical indicators without incorporating individuals' subjective preferences or values, preference-based outcome measures explore how patients (or the general population) assign value to the experience of a specific health state.[53,54] In CUA, the most common way of presenting outcomes is the QALY.[50] The QALY is generated by multiplying health state values with

the amount of time spent in each state, and these results are summed to make the full number of QALYs.[55] The advantage of the QALY as a health output measure lies in its ability to simultaneously encompass morbidity (quality) and mortality (quantity) into a single metric.[50] Less frequently employed CUA measures include the disability-adjusted life year (DALY) and Healthy Years Equivalents.

Same as in CEA, CUA results are expressed as a single outcome, which is the ICER (or the cost per QALY).[50] The primary distinction is that CUA employs QALYs as the denominator when computing the ICER,[56] while in CEA the denominator is a natural unit such as symptom-free days, cases diagnosed, or life-years gained. The cost-effectiveness plane illustrated in Figure 1.1 is also a method for presenting results from a CUA. The threshold for cost per QALY estimates varies based on geographic location when making decisions about allocating resources.[50] When it comes to Canada, CADTH does not officially establish a specific cost per QALY threshold. However, a commonly mentioned benchmark is a threshold of Canadian Dolar (CAD) 50,000 per QALY.[57] NICE has a ‘standard’ threshold of between Great British Pound (GBP) 20,000 to GBP 30,000 per QALY when appraising technologies. However there are certain exceptions.[58] NICE allows a higher threshold of GBP 50,000 per QALY for ‘end-of-life’ technologies, and, in 2017, NICE embraced an elevated threshold ranging from GBP 100,000 to GBP 300,000 per QALY when evaluating treatments designed for "*very rare diseases*".[58]

### *Cost-benefit analysis*

CBA is a type of economic evaluation which compares both costs and benefits of an intervention in monetary terms.[59] In cost-benefit analysis, the decision criterion states that an intervention is deemed cost-effective when its monetized benefits surpass its costs, resulting in a positive net benefit. For example, if benefits are worth USD 140 million, and costs to the society are USD 20 million, it equals USD 120 million in net benefits. In CBA, there needs to be the translation of the benefits of an intervention in monetary values to facilitate meaningful comparison to the program’s costs, which are already expressed in monetary terms.[34] This means that consequences such as life-years gained, disability days avoided, or hospitalizations avoided need to be expressed in monetary terms. CBA is infrequently used in healthcare settings, in comparison to other types of economic evaluations, but is instead more present in areas such as environment economics and transport economics.[34] This is mostly because it is

challenging to place a dollar value on health improvements. For instance, how much someone is willing to pay for health improvement may vary based on individual characteristics, such as their socio-economic status. If interventions are evaluated based solely on their monetary benefits and high-income individuals are willing to pay more for their health improvements, there is a risk that interventions favoured by this demographic might be more likely to be approved. This could potentially exacerbate healthcare disparities.[60]

### *Cost-consequence analysis*

The final type of economic evaluation, CCA, is a method of economic evaluation which presents outcomes, resource use, and costs in a disaggregated form for all groups under comparison.[36] One of the advantages of CCA is that it allows decision-makers to ascribe their values to health outcomes, non-health outcomes and costs, and decide on whether to adopt an intervention based on their own values and their own understandings of the results.[61] Another purported advantage is that it is more transparent, accessible, and easily understandable for decision-makers in comparison to other types of economic evaluations.[62] However, there are several drawbacks of CCA. For example, individual decision-makers may sometimes make choices that do not align with the optimal outcomes for patients or society.[63] The interpretation of CCA results also often involves more subjectivity compared to other types of economic evaluations, creating opportunities for selectively highlighting positive findings, and leading to reporting bias.

## 1.6. Economic evaluation in the context of multimorbidity

Economic evaluations of interventions for managing multimorbidity are sparse. A systematic review from 2023 by Banstola and colleagues included 19 studies and it focused on mental-physical multimorbidity, where one of the chronic conditions have to be a depressive disorder (depression, major depressive disorder, persistent depressive disorder, or dysthymia).[64] Three types of economic evaluations (CUA, CEA, and CBA) were included, and all of them were conducted in high-income countries. The overall

conclusion that the authors had is that most interventions (14 out of the 19) included in the systematic review are potentially cost-effective.

Another recent systematic review explored economic evaluations of treatments for optimizing medication use in older adults with multimorbidity and polypharmacy, and 11 studies were included.[65] Same as the review by Banstola et al.,[64] CEA, CUA, and CBA were included, and all were conducted in high-income countries. According to the authors, given the heterogeneity in reported outcomes and the low quality of the economic evaluations, it was not possible to reach a definitive conclusion regarding the cost-effectiveness of interventions aimed at optimizing medication use in the context of multimorbidity and polypharmacy.

### 1.6.1. Internet chronic disease management (iCDM) program for multimorbidity: randomized controlled trial

Chapter 3 in this thesis is an economic evaluation of a DHI targeted for patients with multimorbidity. The economic evaluation in Chapter 3 was conducted using data from an (RCT) that assessed the impact of the iCDM program on both costs and outcomes. In the trial, 116 patients were assigned to the treatment arm and received iCDM intervention, while the control arm consisted of 113 patients who received usual care only. More details of the trial are provided in Chapter 3.

## 1.7. Objectives

This MSc thesis is focused on individuals with multimorbidity. The objectives are to: 1) systematically identify and synthesize the costs and benefits associated with interventions targeted to people living with multimorbidity (Chapter 2), and 2) undertake a CCA to determine costs and outcomes of iCDM intervention for adults with multimorbidity using data from an RCT (Chapter 3). Chapter 4 concludes the thesis by summarizing the key findings, outlining the novelties and significance of the research, and suggesting areas for future exploration.

# Chapter 2.

# Economic evaluations of interventions for people with multimorbidity: a systematic literature review

## 2.1. Introduction

As discussed in Chapter 1, multimorbidity refers to the simultaneous presence of two or more chronic diseases in an individual, where none of the conditions necessarily holds greater significance than the others. Several systematic reviews have sought to synthesize evidence for interventions designed for people with multimorbidity, with research questions focusing on whether the interventions improve outcomes[33,66–68] or reduce healthcare utilization.[67,69] Relatively few reviews have explored the question of cost-effectiveness, where the *joint estimation* of costs and outcomes are examined. Previous systematic reviews of economic evaluations have adopted alternative definitions of multimorbidity.[64,65] For example, a 2023 systematic review by Banstola et al., defined multimorbidity as the co-occurrence of two or more long-term chronic diseases in the same individual (and the specific context of their review was "*mental-physical multimorbidity that includes a depressive disorder*").[64] Another systematic review, published in 2021, adopted a similar definition of multimorbidity, this time focusing on interventions to optimize medication use for older adults with both multimorbidity and polypharmacy.[65] The distinguishing feature between the definition used in these two reviews and the one explored in this thesis is that no single chronic condition should be considered more significant than the other(s) within an individual's health profile. The definition used in this thesis has been adopted from the paper discussing the future of multimorbidity by Cynthia M. Boyd and Martin Fortin.[3]

As mentioned in Chapter 1, while assessing the outcomes is less challenging when it comes to comorbidity-focused interventions, the evidence regarding their cost-effectiveness is inconclusive. According to the definition of multimorbidity used in this thesis, both the systematic reviews by Banstola et al.[64] and Laberge et al.[65] mainly included economic evaluations of comorbidity-focused interventions. Although some

interventions were found to be potentially cost-effective in Banstola et al., no overall cost-effectiveness conclusion can be drawn.[64] According to Laberge et al., the heterogeneity in reported outcomes and the low quality of the economic evaluations included in their review made it impossible to reach a definitive conclusion regarding the cost-effectiveness of multimorbidity interventions.[65] Based on current literature, which is primarily focused on the cost-effectiveness of comorbidity-focused interventions, it is unclear whether interventions seeking to manage multimorbidity are cost-effective.

The objective of this study is to systematically identify and synthesize the costs and benefits associated with interventions targeted to people living with multimorbidity by conducting a systematic literature review of economic evaluations of multimorbidity-focused interventions. In this review, multimorbidity refers to the presence of two or more chronic conditions in a single person, where the conditions are considered equally important, with none being the dominant one.

## 2.2. Methodology

This systematic review is registered in the PROSPERO database (CRD42023402880).[70]

### 2.2.1. Search strategy

The search strategy was developed to identify peer-reviewed economic evaluations for interventions in the context of multimorbidity. The search strategy consisted of two parts, with search terms relating to (i) the study design (i.e., economic evaluation) and (ii) the clinical context (multimorbidity). Twelve databases were searched using a timeframe of January 1, 1990 to February 28, 2023: MEDLINE; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Methodology Register; Database of Abstracts of Reviews of Effects (DARE); Cochrane Clinical Answers; ACP (American College of Physicians) Journal Club; Health Technology Assessment (HTA); NHS EED; Cumulative Index to Nursing and Allied Health Literature Complete (CINAHL Complete); PsycINFO; and Excerpta Medica Database (EMBASE). A reference list search of included studies was also conducted along with a forward citation search. The full search strategy, as used in MEDLINE on

the Ovid platform, is provided in Appendix A.1. Search terms related to economic evaluation (lines #1 to #16 in Appendix A.1) were adopted from a systematic review that identified, documented, and appraised studies that reported on the cost-effectiveness of non-invasive and non-pharmacological treatments for low back pain.[71] This paper was chosen since it had search terms for different components of economic evaluation (e.g., healthcare costs) as well as different economic evaluation designs (e.g., cost-utility analysis). Search terms related to multimorbidity (lines #20 to #43 in Appendix A.1) were adopted from a 2022 systematic review and meta-analysis which explored the association between multimorbidity and hospitalization in older adults.[72] Search terms for 'comorb*' (line #18) and 'co-morb*' (line #19) were added to the search strategy. The decision to include comorbidity-related terms was made because of the relatively recent (2018) creation of separate MeSH headings for multimorbidity and comorbidity. An SFU liaison librarian, Hazel Plante, was consulted on search strategy-related aspects, such as providing appropriate resources on how to build a search strategy and selecting appropriate databases.

### 2.2.2. Exclusion criteria & screening

The screening of identified records was conducted in two stages (see Table 2.1). Stage 1 comprised title and abstract screening only (performed in Covidence),[73] completed by the candidate (reviewing 100% of the identified studies) and four other members of the research team (Dr. David Whitehurst, Dr. Helen McTaggart-Cowan, Nazafarin Esfandiari, and Muntasir Rahman) (each reviewing 25% of the identified studies). Stage 2 involved full text screening, which was performed, independently, by the candidate and the candidate's supervisor, with both people reviewing all identified studies from Stage 1. Agreement between reviewers was explored by recording the number of times reviewers came to the same decision (independently) about whether to include or exclude a particular study. Disagreements at each stage were resolved through discussion between reviewers.

**Table 2.1: Exclusion criteria for Stage 1 and Stage 2 of screening.[a]**

| Stage 1 | Stage 2[b] |
|---|---|
| 1: Abstract-only publication | 1: Abstract-only publication |
| 2: Not published in a peer-reviewed journal | 2: Not published in a peer-reviewed journal |
| 3: Not in English language | 3: Not in English language |
| 4: No reference to an ***economic evaluation*** conducted by the authors | 4: No reporting of an ***economic evaluation*** conducted by the authors |
| 5: Clinical context does not include individuals with two or more chronic conditions | 5: Intervention was not specifically managing or treating ***multimorbidity*** |
| 6: Explicit statement alluding to treatment of one of the chronic conditions being the focus of the study | 6: Majority of the study sample were not individuals living with ***multimorbidity*** |

[a] Text in bold italics indicates words/phrases defined on page 9 (economic evaluation) and page 1 (multimorbidity). The definitions for both terms were different in Stage 1 and Stage 2.
[b] The reasons for exclusion were documented at Stage 2 only. To facilitate this, Stage 2 exclusion criteria were considered in the order presented above, with the assigned reason for exclusion reflecting the order. For example, a record that could be excluded for criteria #3 and #5 would be categorised as being excluded based on criterion #3.

In Stage 1, consideration of 'economic evaluation' (criterion #4) was applied broadly, with the title and/or abstract only having to give an indication the paper included information about the costs and outcomes of an intervention. For the clinical context in Stage 1 (criteria #5 and #6), the WHO's definition of chronic disease was used to define chronic conditions ("*health problems that require ongoing management over a period of years or decades*").[74] For verification purposes, the first three exclusion criteria of Stage 2 were the same as Stage 1. Criteria #4 to #6 in Stage 2 were where more specific definitions of economic evaluation (criterion #4) and multimorbidity (criterion #5 and #6) were applied—definitions that were possible to confirm because the full texts of articles were being screened. For papers to be considered as economic evaluations, they needed to be CEA, CUA, CCA, or CBA. Papers were also excluded if it was confirmed 50% or more of the participants in the study did not have multimorbidity. Additionally, if the intervention was not specifically managing or treating multimorbidity, the paper was excluded. The clinical context in Stage 2 needed to include individuals living with multimorbidity. Therefore, if a study included participants with comorbidity with a primary medical condition, the paper was excluded.[75] It was possible that the definition of multimorbidity used in this review – *two or more chronic conditions, one not necessarily more important than the other(s)* – would not be used explicitly in studies. In such circumstances, screeners were required to use their judgment to see whether the details reported in the paper met the definition.

### 2.2.3. Data extraction & synthesis

Data extraction was performed by the candidate (100% of the studies) and the candidate's supervisor (25% of the studies). Table 2.2 provides details of the categories of information that were extracted, broadly categorized in three groups: (i) general characteristics, (ii) methodological details, and (iii) results/findings from the economic evaluation. A narrative synthesis of the findings was used to outline the general characteristics, methodological details, and economic evaluation results, as well as quality assessment aspects of the included studies (described further in Section 2.2.4).

The presentation of results focused on the number of identified economic evaluations (i.e., the unit of analysis was the number of economic evaluations rather than the number of identified papers). For presentation purposes, syntheses of economic evaluation results were reported by intervention type. Categorization of interventions (except care coordination only) was adopted from a systematic review that focused on interventions for improving outcomes in patients with multimorbidity in primary care and community setting.[24] Interventions were classified as follows, based on the main intervention focus: (i) care coordination plus self-management support; (ii) self-management support only, (iii) medicine management; and (iv) care coordination only. Care coordination was added to the classification because the preliminary full text screening of the included studies pointed out that some interventions will not fall into the first three categories.

Based on the Second Panel on Cost-Effectiveness in Health and Medicine's recommendations, resource use items were categorized in terms of (i) formal healthcare sector costs (medical costs), including future related and unrelated medical costs paid by third-party payers or out-of-pocket by patients themselves; (ii) informal costs, such as nonpaid caregiver time, patient time, and transportation costs; and (iii) non-healthcare costs, such as cost of social services and productivity losses.[35] To facilitate the comparison of different interventions for multimorbidity, the incremental costs and ICERs were converted into 2023 USD using the Campbell and Cochrane Economics Methods Group (CCEMG) Evidence for Policy and Practice Information and Coordinating Centre Cost Converter online tool.[76]

**Table 2.2: Description of data extraction categories.**

| Data extraction category | Explanation |
|---|---|
| *General characteristics* | |
| Lead author (year) | Last name of the lead author, and year of publication in the journal article |
| Location | Country or region in which the economic evaluation was conducted |
| Intervention delivery setting (number of participants) | Type of setting in which the study has occurred and number of people who were analyzed in the economic evaluation regardless of what authors did when it comes to missing data |
| Multimorbidity definition | The definition of multimorbidity used by the authors |
| *Methodological details* | |
| Economic evaluation type (trial-based/model-based) | Classification of economic evaluation type based on what authors said in the paper (trial-based or model-based economic evaluation) |
| Perspective | Economic evaluation perspective based on "*Perspective and Costing in Cost-Effectiveness Analysis*" paper written by Kim et al.[38] |
| Time horizon, discount rate | Trial-based: length of follow-up; Model-based: time horizon. If discounting was applied, discount rate reported |
| Resource use items | Type of resource use items included in the economic evaluation based on the Second Panel on Cost-Effectiveness in Health and Medicine's recommendations |
| Currency, reference year | Currency used in the study, and its reference year. When the reference year was not reported, the year of study publication was used to convert the currency to 2023 United States Dollar (USD) |
| Outcome(s) (measure(s)) | Type of outcome(s) and measure(s) examined in the study |
| *Results/findings from the economic evaluation* | |
| Reported conditions of participants | Type of conditions of study population |
| Incremental cost | How much intervention costs versus how much comparator costs (based on what authors said). Costs reported in original study were converted to 2023 United States Dollar (USD) |
| Incremental effect | Difference in outcome(s) between intervention and comparator (based on what authors said) |
| Base case analysis ICER | ICER results depending on the type of economic evaluation (based on what authors) |
| Sensitivity analysis | Results of the sensitivity analysis (based on what authors said) |

| Data extraction category | Explanation |
|---|---|
| Author's conclusions | Author's conclusions about cost-effectiveness |

ICER indicates incremental cost-effectiveness ratio; USD, United States Dollar.

Four study perspectives were considered based on the "*Perspective and Costing in Cost-Effectiveness Analysis*" paper written by Kim et al.,[38] where 'perspective' refers to the viewpoint chosen when determining which outcomes and costs are relevant for inclusion. First, healthcare payer, where costs are incurred by healthcare payer. Second, the healthcare sector, which is similar to the healthcare payer perspective but accounts for all costs of healthcare, regardless of who bears the cost. Third, limited societal, where costs are captured beyond those captured by the healthcare sector perspective, such as patient time, patient transportation, productivity loss, and unpaid caregiver time. Fourth, the societal perspective, which is broader than the limited societal perspective, and takes into account the overall public interest by including all resources that could be used for other purposes, and considers cost impacts on additional sectors like the environment or education.[38]

### 2.2.4. Quality of reporting of the studies

The reporting standards and quality appraisal of identified economic evaluations were assessed by using the 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) and the Quality of Health Economic Studies (QHES) instrument.[77,78] The CHEERS 2022 statement consists of 28 items that appraises an article on the following sections/topics: title (1 item); abstract (1 item); introduction (1 item); methods (18 items); results (4 items); discussion (1 item); and 'other relevant information' (namely, funding source and conflicts of interests) (2 items). Scoring was marked using 'yes' (reported in full), 'no' (not reported or partially reported), or 'NA' (not applicable). Descriptions of the 'guidance for reporting' each item, as described by the CHEERS 2022 ISPOR Good Research Practices Task Force, are provided in Appendix A.2. The QHES includes 16 yes/no questions that consist of assessments of the study objectives, perspectives, data sources, subgroup analysis, sensitivity analysis, costs, outcome measures, time horizons and discount rates, model structure, potential biases,

and recommendations.[78] The cumulative scores of the questions yield a total summary score that ranges from 0 to 100 points, and studies are considered high quality if they achieved a score of 75 or above.[78] A recent study introduced modifications to the QHES tool, enhancing its grading system and flexibility in assessing studies with varying characteristics, including the addition of 'none' as a scoring option to all questions.[79] The modified QHES was used in this review; the modified QHES questions and scoring procedure are provided in Appendix A.3. In the paper by Marshall et al., the quality of economic evaluations of clinical nurse specialists and nurse practitioners was assessed with the QHES tool.[80] To ensure consistent interpretation, the authors provided specific guidance for each QHES question. In this systematic review, specific guidance from the study by Marshall et al. was used to ensure consistent interpretation for each QHES question.

## 2.3. Results

### 2.3.1. Study selection

A total of 20,413 records were identified from the 12 databases, of which 7,851 were duplicates (Figure 2.1). In Stage 1, the remaining 12,562 titles and abstracts were screened, and 12,457 were excluded. During Stage 2, 104 full texts were screened, and 15 were considered suitable for inclusion. At Stage 2, one paper could not be accessed through the Simon Fraser University (SFU) library databases and therefore was removed from the review. One additional record was identified from the reference lists and a forward citation search of the included studies. Agreement between reviewers was 95.9% (12,040/12,562) in Stage 1 and 98.1% (103/105) in Stage 2. A total of 16 studies (from which 17 economic evaluations were identified) were included in the review.

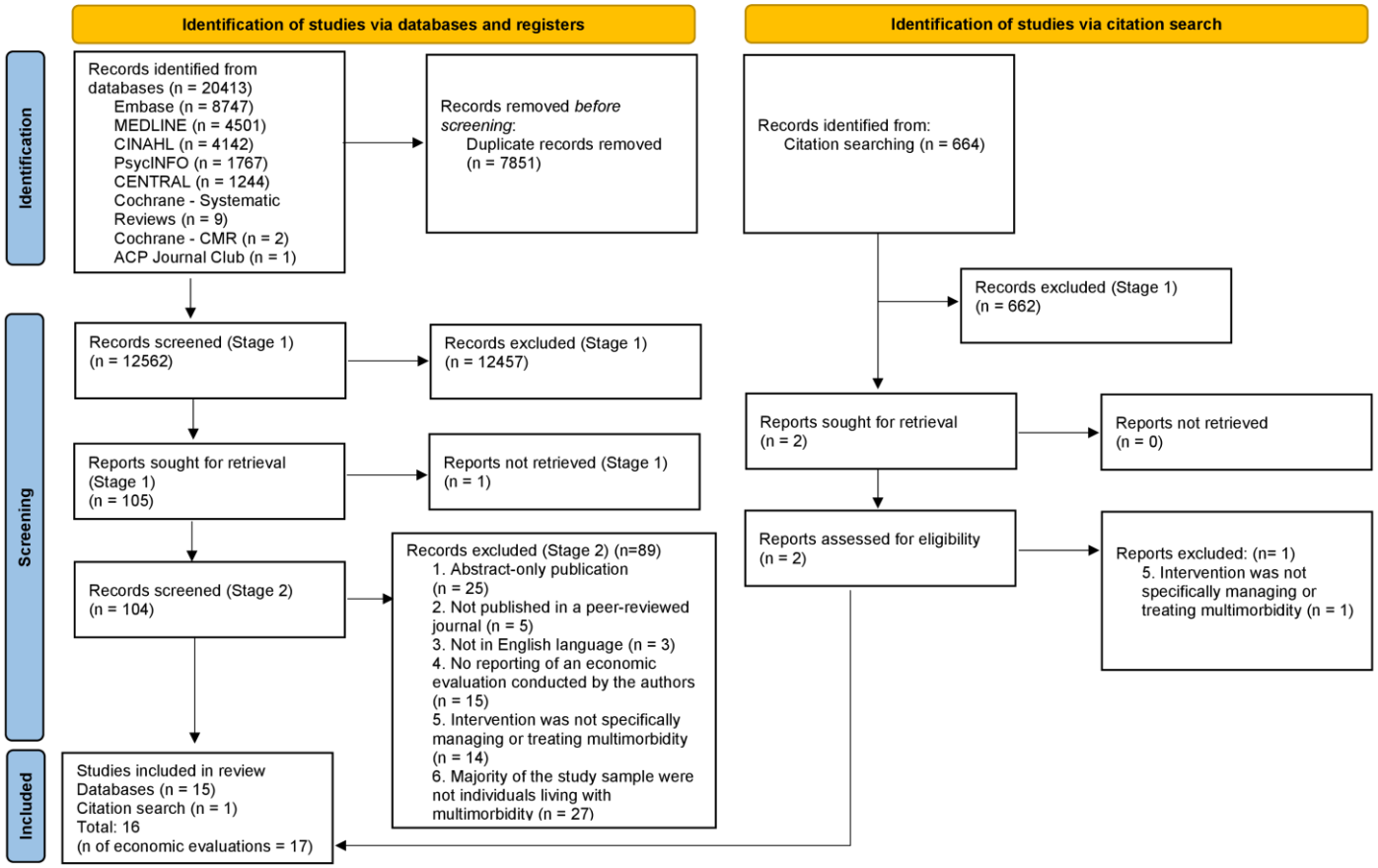


**Figure 2.1: PRISMA flow diagram for the systematic review**

## 2.3.2. Study characteristics

The characteristics of the economic evaluations are summarized in Table 2.3. All 17 economic evaluations were conducted in high-income countries, 15 of them in only one country,[81–94] and two in two or more countries.[95,96] Fourteen economic evaluations were undertaken in Europe (82.4%)[82–90,92,93,95,96] (England (n=4)[84,92,96] was the country where the most economic evaluations came from), and three were done in North America (17.6%).[81,91,94] The intervention delivery setting that was most common was primary care (n=7),[86–88,90,91,96] followed by ambulatory geriatric units (n=3),[82,83,89] and clinical centres (n=2),[94,95]. All economic evaluations except one[89] reported the number of participants, and the number of participants in the economic evaluations ranged from 45[91] to 2008.[95]

Multiple definitions of multimorbidity were used. The most common definition was based on having two or more chronic conditions.[81,85,86,90,94] Only one study defined multimorbidity as it was defined in this review: *the presence of two or more chronic conditions, where one is not more important than the others*.[92]

## 2.3.3. Details of the adopted methods

Table 2.3 also provides information about the methodological details of the included economic evaluations. Of the 17 economic evaluations, 10 were CUAs (58.8%).[81,86–92,95,96] In CUAs, the most commonly used generic measure were different versions of EQ-5D (n=8),[81,86–89,91,95,96] one study used SF-6D,[87] and another study used Assessment of Quality of Life four-dimension questionnaire (AQoL-4D).[91] This was followed by CCAs (n=4, 23.5%),[82,83,93,96] which examined the range of outcomes, the most frequent ones being hospital length of stay (n=3)[82,83,93] and number of hospitalizations (n=3).[82,83,93] Three economic evaluations used a CEA design (17.6%),[84,85,94] and the only outcome was change in HRQoL.

**Table 2.3: General characteristics and methodological details of included economic evaluations.**

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Basu (2015)[81] | US | Workshops delivered nationwide by 22 licensed sites (1170) | Having at least two chronic conditions | CUA (RCT) | Not reported | 1 year, NA | Formal healthcare sector: workshop sessions, peer personnel, materials, training space, ED visits, hospitalizations | USD, not reported | QALYs (EQ-5D: no version stated), HRQoL (EQ-5D: no version stated), healthy days (no measure stated) |
| Ekdahl (2015)[82] | SWDN | Ambulatory geriatric unit (382) | No clear definition | CCA (RCT) | Not reported | 2 years, not reported | Formal healthcare sector: visits to physicians and other staff, hospital-based home healthcare, hospital care, operative and ICU care, laboratory, pharmaceuticals, helping aids, home help services, institutional living | GBP, 2013 | HRQoL (EQ-5D-3L), number of hospitalizations, hospital length of stay, nursing home admittance, mortality rates, participant' sense of security in care (SEC-P[b]) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Ekdahl (2016)[83] | SWDN | Ambulatory geriatric unit (382) | No clear definition | CCA (RCT) | Not reported | 3 years, not reported | Formal healthcare sector: visits to physicians and other staff, hospital-based home healthcare, hospital care, operative and ICU care, laboratory, pharmaceuticals, helping aids, home help services, institutional living | USD, 2014 | Number of hospitalizations, hospital length of stay, nursing home admittance, mortality rates |
| Evans (2021)[84] | ENG | Primary care and community care (48) | No clear definition of multimorbidity but it mentions complex multimorbidity which is described as four or more conditions present in an individual | CEA (RCT) | Not reported | 12 weeks, NA | Formal healthcare sector: palliative care team, community healthcare, primary care, equipment<br>Informal: informal care<br>Non-healthcare: social care | GBP, 2019 | Changes in HRQoL (EQ-5D-5L), five key symptoms (IPOS-5[c]), and caregiver burden (self-assessed short form Carer Zarit Burden Interview[d]) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Gayot (2022)[85] | FRAN | Nursing home (426) | Having at least two chronic diseases | CEA (RCT) | Healthcare payer | 1 year, NA | Formal healthcare sector: consultations, teleconsultations, unplanned hospitalizations, ED admissions, transportations | USD, not reported | Proportion of patients with unplanned hospitalizations, participants with and number of unplanned hospitalizations, length of hospital stay, ED admissions, consultations by physician, deaths, HRQoL (EQ-5D: no version stated) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Gillespie (2022)[86] | IRE | Primary care (149) | The presence of two or more chronic diseases | CUA (RCT) | Healthcare payer | 6 months, NA | Formal healthcare sector: GP visits: outpatient visits, inpatient days, accident and emergency visits; educator and administrator time input, healthcare professional time input, educational materials and consumables, post, packaging, telephone, travel expenses | EUR, 2019 | QALYs, HRQoL (EQ-5D-3L) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Kari (2022)[87] | FIN | Primary care (277) | No clear definition | CUA (RCT) | Healthcare payer | 2 years, not reported | Formal healthcare sector: GP and nurse: planned appointment, home visit, phone call; physiotherapist and occupational therapists: appointments; speech therapist and rehabilitation assistant: appointments, phone call; health centre assistant: phone call; primary care ward day, polyclinic diagnostic operations | EUR, 2017 | QALYs (SF-6D), physical performance (Short Performance Physical Battery (SPPB)[e]), physical dimension component summary score and changes in HRQoL (SF-36) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Lanzeta (2016)[88] | SPN | Primary care (140) | No clear definition | CUA (RCT) | Not reported | 1 year, NA | Formal healthcare sector: hospital admissions, ED attendances, visits to specialists, primary care doctors, nurses and diagnostic tests | EUR, not reported | QALYs, HRQoL (EQ-5D: no version stated) |
| Lundqvist (2018)[89] | SWDN | Ambulatory geriatric unit (not reported) | No clear definition | CUA (Markov model) | Healthcare sector | 30 years, 3% | Formal healthcare sector: primary healthcare, ambulatory care (geriatric and other), inpatient care and municipal services (home help and nursing home) | EUR, 2016 | QALYs (EQ-5D-3L), life years |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Mercer (2016)[90] | SCT | Primary care (225) | Having two or more long-term conditions | CUA (RCT) | Healthcare payer | 1 year, NA | Formal healthcare sector: all consultations within the practice, and all out-patient consultations and in-patient admissions | GBP, 2011/12 | QALYs and changes in HRQoL (EQ-5D-5L); wellbeing and energy (W-BQ12[f]), self-esteem, self-efficacy, anxiety and depression (Hospital Anxiety and Depression Scale (HADS)[g]) |
| Miranda (2022)[91] | CAN | Primary care (45) | Having multiple chronic conditions | CUA (Decision tree) | Healthcare payer | 15 months, not reported | Formal healthcare sector: technology support, training, and licensing, communication, onboarding management, app modification, feature development, professional services support | CAD, 2020 | QALYs (Assessment of Quality of Life 4-Dimension (AQoL-4D)[h]) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Panagioti (2018)[92] | ENG | Remote: the intervention was delivered via telephone from a central NHS facility (1306) | The presence of two or more chronic conditions, where one is not more important than the others | CUA (trial within cohort) | Healthcare sector | 20 months, 3.5% | Formal healthcare sector: training and supervision, written materials and delivery of the health coaching session, ED admission and stay, primary care visit | GBP, 2014/15 | QALYs and HRQoL (EQ-5D-5L), self-management (PAM[j]), WHO quality of life ( WHOQOL-BREF[k]), depression (MHI-5[l]), self-care (SDSCA[m]) |
| Salari (2022)[95] | SWTZ, BELG, IRE, NETH | Clinical centres (2008) | The presence of three or more chronic conditions | CUA (RCT) | Healthcare sector | 1 year, NA | Formal healthcare sector: hospitalizations, rehabilitation facilities, medical visits, nursing home care and visits and drugs | CHF, 2018 | QALYs (EQ-5D-5L) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Thorn (CUA) (2020)[96] | ENG and SCT | Primary care (1546) | Having multiple chronic conditions | CUA (RCT) | Healthcare sector (NHS/PSS) | 15 months, 3.5% | Formal healthcare sector: practice-based consultations, investigations, community-based healthcare, inpatient stays, outpatient visits and day cases, accident and emergency visits, ambulance trips to hospital, prescribed medications, pharmacy reviews, intervention set up<br>Non-healthcare: social services | GBP, 2015/16 | QALYs (EQ-5D-5L) |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Thorn (CCA) (2020)[96] | ENG and SCT | Primary care (1546) | Having multiple chronic conditions | CCA (RCT) | Limited societal (NHS/PSS, patient/ carer, productivity) | 15 months, 3.5% | Formal healthcare sector ones above + prescription charges, over-the-counter medications, private healthcare<br>Informal: travel to GP<br>Non-healthcare: productivity loss, social services | GBP, 2015/16 | QALYs (patient, carer) (EQ-5D-5L), number of deaths |
| Vila (2015)[93] | SPN | Primary care and clinical centre (293) | Having multiple chronic conditions | CCA (RCT) | Not reported | 2 years, not reported | Formal healthcare sector: hospitalization, ED visits, ambulance, EHCs, tests, specialist fees, home oxygen therapy, laboratory tests, primary care physician fees, rehabilitation, program resources | EUR, not reported | Hospital length of stay, number of hospitalizations, number of deaths, ED visits, EHCs |

| Lead author (year) | Location | Intervention delivery setting (# of participants) | Multimorbidity definition | EE type (trial-based /model-based) | Perspective | Time horizon, discount rate | Resource use items | Currency, reference year[a] | Outcome(s) (measure(s)) |
|---|---|---|---|---|---|---|---|---|---|
| Zimmerman (2017)[94] | US | Clinical centre (126) | Having two or more chronic conditions | CEA (RCT) | Healthcare payer[n] | 6 months, NA | Formal healthcare sector: staff time allocated to home visits, phone calls, predischarge education, ED and inpatient setting stay | USD, not reported | Changes in health-related quality of life (EQ-5D: no version stated) |

BELG indicates Belgium; CAD, Canadian Dollar; CCA, cost-consequence analysis; CUA, cost-utility analysis; ED, emergency department; EE, economic evaluation; EHC, emergency house call; ENG, England; EUR, Euro; FIN, Finland; FRAN, France; GBP; Great British Pound; GP, general practice; HRQoL, health-related quality of life; ICU, intensive care unit; IPOS, Integrate Palliative care Outcome Scale; IRE, Ireland; NA, not applicable; NETH, Netherlands; NHS. National Health Service; PSS, Personal social services; QALYs, quality-adjusted life years; RCT, randomized controlled trial; SCT, Scottland; SPN, Spain; SWDN, Sweden; SWTZ, Switzerland; US, United States; USD, United States Dollar; WHO, World Health Organization.

[a] When the reference year was not reported, the year of study publication was used to convert the currency to 2023 United States Dollar (USD).
[b] The Sense of Security in Cared Patients' Evaluation instrument has three scales: care interaction (eight items), identity (four items), and mastery (three items). Responses are structured by a 6-point Likert scale (1= never, 6 = always).
[c] The five key symptoms (pain, breathlessness, patient anxiety, drowsiness and constipation) were measured using IPOS-5 (Integrated Palliative care Outcome Scale). Total score ranges from 0 to 20.
[d] The self-assessed short form Carer Zarit Burden Interview is a 12-item short form often used as a caregiver self-report measure.
[e] SPPB is a measure of physical function in clinical and community settings. It consists of three timed components (balance, five-times repeated chair sit-to-stand, and usual-pace gait speed) which measure balance, lower body muscle strength and mobility.[97] Lower scores tend to predict lower quality of life, loss in mobility, disability and mortality.
[f] The W-BQ12 has three components measured in its 12 items: negative wellbeing, positive wellbeing, and energy. The component scores can be combined to give an overall general wellbeing score.
[g] Hospital Anxiety and Depression Scale is a self-report rating scale of 14 items on a four-point Likert scale (range 0–3). It measures depression and anxiety (seven items for each subscale). The total score is the sum of the 14 items, and for each subscale the score is the sum of the seven items ( from 0–21).[98]
[h] The AQoL-4D contains four dimensions: independent living, social relationships, physical sense, and psychological wellbeing.[99] There are three items in each dimension. The AQoL-4D questionnaire can be used as a psychometric measure or as a multi-attribute utility measure. When used as a utility measure, a utility formula is used to convert item responses into a global utility score on a 0.00 (dead) to 1.00 (full health) scale, with higher scores indicating a better outcome.

[i] A cohort was recruited, and a trial was conducted using a randomly selected group within the cohort.
[j] The PAM is a self-report measure of patient knowledge, skills and confidence in self-management for long-term conditions. The authors used the short 13-item version.
[k] WHOQOL-BREF is a 26-item measure of global quality of life, which is validated in a large international population with physical and mental long-term conditions. Quality of life is measured across four domains: physical, psychological, social and environmental, as well as a single-item scale for quality of life.
[l] MHI-5 is a five-item scale which measures general mental health. This measure is validated for identifying depression symptoms, with a higher score indicating better mental health.
[m] SDSCA is a seven-item measure assessing the number of days per week respondents engage in healthy and unhealthy behaviours, such as eating fruits and vegetables, eating red meat, undertaking exercise, drinking alcohol and smoking.
[n] Authors claimed that analysis was conducted from a societal perspective; however, based on resource use items included in the study it is clear that the study was not conducted from the stated perspective

Trial-based analyses accounted for 15 out of 17 economic evaluations (88.2%),[81–88,90,92–96] while model-based analyses accounted for two out of 17 (11.8%).[89,91] Among trial-based evaluations, the data source for 14 of them were RCTs (93.3%),[81–88,90,93–96] as well as trial within a cohort for one economic evaluation.[92] The two model-based economic evaluations comprised a decision tree (n=1),[91] and a Markov model (n=1).[89]

The majority of economic evaluations (n=11, 64.7%) reported the study perspective.[85–87,89–92,94–96] Among the 11 economic evaluations that reported the study perspective, the most common was the healthcare payer perspective (n=6),[85–87,90,91,94] followed by the healthcare sector perspective (n=4).[89,92,95,96] One study was conducted from both the healthcare sector and limited societal perspective (n=1).[94,96]

It should be noted that in one paper authors claimed that analysis was conducted from a societal perspective, but based on resource use items included in the study it was clear the study was not conducted from the stated perspective and was instead conducted from a healthcare payer perspective.[94]

Most economic evaluations included in this review adopted a one-year (n=5)[81,85,88,90,95] or two-year (n=3)[82,87,93] time horizon. Some economic evaluations used longer time horizons, such as three years[83] or 30 years.[89] However, some used shorter time horizons such as six months[94] or 12 weeks.[84]

The majority of the economic analyses (n=14, 82.4%)[81–83,85–95] only considered formal healthcare costs (i.e., hospitalizations, nursing home, primary care, and emergency department (ED) visits). Three (17.6%) economic evaluations also considered non-healthcare costs,[84,96] such as social care[84,96] and productivity impacts,[96] and two examined informal costs,[84,96] such as informal care[84] and travel to a general practitioner.[96]

## 2.3.4. Results/findings from economic evaluations

The results/findings of the economic evaluations are reported in Table 2.4. Six (35.3%) of the 17 economic evaluations involved care coordination plus self-management support type interventions.[87,88,90,94,96] Another six (35.3%) examined care coordination

type interventions and involved interventions that targeted geriatric and palliative multimorbid adults.[82–85,89,93] Four (23.5%) economic evaluations reported on self-management support type interventions.[81,86,91,92] One economic evaluation (5.9%) involved an intervention primarily focused on medicines management but specifically targeted patients with multimorbidity.[95] Additional details about the nature of the interventions included are provided in Appendix A.4.

The majority of economic evaluations (n=12)[81–85,87,90,93–96] reported the specific conditions that patients had. The most common conditions examined were depression (n=7)[81,85,87,90,93,96] and diabetes (n=7).[82–85,89,93]

### *Care coordination plus self-management support interventions*

The majority of care coordination plus self-management support interventions (66.7%) were found to be cost-effective. A CUA alongside an RCT, from Scotland, found that a primary care-based intervention to improve quality of life in multimorbid patients had an ICER of Great British Pound (GBP) 12,224 (USD 22,338.82) per QALY gained.[90] This is lower than the threshold range of GBP 20,000-GBP 30,000 per QALY gained used by NICE.

A trial-based CUA from Finland found that a people-centred care model is dominant in comparison to usual care.[87] A study from England and Scotland reported both CUA and CCA.[96] The CUA alongside an RCT found that an intervention which involves patient-centred care with coordination between a multidisciplinary team of nurses, pharmacists, and a physician, compared with usual care, had an ICER of GBP 18,499 (USD 29,694.29) per QALY gained,[96] (again, lower than the threshold range used by NICE).

**Table 2.4: Results/findings from economic evaluations.**

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| **Care coordination plus self-management support interventions** | | | | | | |
| Kari (2022)[87] | Hypertension, HF, arrhythmia, hypercholesterolemia, diabetes, impaired fasting glucose, hypothyroidism, cancer, asthma, COPD, Alzheimer disease, depression | EUR -2,139 (USD -2,642.13) | QALYs: 0.029<br>Physical performance[c]: 0.27<br>Physical component summary score: -1.81<br>Changes in HRQoL: 0.01 | Intervention dominant | DET: The effects of inflating the usual care costs by lowering them by 20% were examined, and the results reflect those from the base case analysis | Intervention was dominant |
| Lanzeta (2016)[88] | Not reported | EUR 1,035.90 (USD 1,807.06) | QALYs: − 0.07; not reported for other outcome | Intervention dominated | PROB: For the subgroup of people under 80 years of age with three or more conditions, intervention resulted in cost saving in 89% of the simulations | Intervention was not cost-effective |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| Mercer (2016)[90] | Anxiety, depression, HBP, back problems, arthritis, asthma, diabetes, angina, heart attack, migraine, IBS, eczema /psoriasis, chronic bronchitis, stroke, mini-stroke, thyroid problem, kidney, and liver disease, cancer, HF | GBP 929 (USD 1,697.75) | QALYs: 0.076<br>General wellbeing[d] : 1.99<br>Negative wellbeing: -1.30<br>Energy: 0.31<br>Positive wellbeing: 0.57<br>Self-efficacy: 0.07<br>Self-esteem: 0.74<br>Anxiety: - 0.91<br>Depression: -1.25<br>Changes in HRQoL: 0.06 | GBP 12,224 (USD 22,338.82) per QALY gained | PROB: Modelling of estimated effects two years beyond the trial period suggested that this cost-effectiveness would be likely to continue in the longer term | Intervention was potentially cost-effective |
| Thorn (CUA) (2020)[96] | Cardiovascular disease, stroke, transient ischemic attack, diabetes, COPD, asthma, epilepsy, mental illness, depression, dementia, learning disability, RA | GBP 126 (USD 207.86) | QALYs: 0.007 | GBP 18,499 (USD 29,694.29) per QALY gained | DET: The complete-case analysis suggested that intervention was dominant. Excluding participants who died suggested that the probability of cost-effectiveness of intervention at GBP 20,000 was 0.561. Using undiscounted costs and outcomes did not suggest that the discount rate affected the conclusions | There is just over a 50% chance of cost-effectiveness of intervention at the established threshold of GBP 20,000 per QALY from the NHS/PSS perspective |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| Thorn (CCA) (2020)[96] | Cardiovascular disease, stroke, transient ischemic attack, diabetes, COPD, asthma, epilepsy, mental illness, depression, dementia, learning disability, RA | Healthcare sector: GBP – 183 (USD – 301.90) Limited societal (patient/carer): GBP 33 (USD 54.44) Limited societal (productivity loss): GBP 39 (USD 64.33) | QALYs (patient): 0.003 QALYs (carer): - 0.024 Deaths: 46 vs 32 | NA | Not reported | Not reported |
| Zimmerman (2017)[94] | Hypertension, osteoarthritis, hyperlipidemia, diabetes, and COPD | Group 1: USD 489 (USD 552.54) Group 2: USD 351 (USD 396.61) Group 3: USD 286 (USD 323.16) Group 4: USD 75 (USD 84.74) | Changes in HRQoL[e]: Group 1: - 0.17 Group 2: 0.02 Group 3: 0.01 Group 4: 0.02 | Group 1[g]: USD -2,929 (USD -3,309.57) Group 2: USD 18,069 (USD 20,416.76) Group 3: USD 22,520 (USD 25,446.09) Group 4: USD 3,510 (USD 3,966.06) | Not reported | There was a support for cost-effectiveness for Group 2, Group 3, and Group 4 patients[e] |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| **Care coordination interventions** | | | | | | |
| Ekdahl (2015)[82] | Diseases: blood and blood-forming organs, nervous, circulatory, respiratory, digestive, nutritional, metabolic system, infectious, parasitic, Disorders: mental, behavioural, immune system, endocrine | GBP 33,371 vs 30,490 (USD 57,397.22 vs 52,441.98) | HRQoL: Baseline: 0.62 vs. 0.63, Follow-up: 0.60 vs 0.62<br>Care interaction score: Baseline: 4.60 vs 4.67, Follow-up: 5.27 vs 4.70<br>Mastery scale: Baseline: 4.67 vs 4.80, Follow-up: 5.06 vs 4.96<br>Identity scale: Baseline: 5.32 vs 5.33, Follow-up: 5.30 vs 5.21<br>Number of hospitalizations: 2.1 vs 2.4<br>Inpatient days: 11.1 vs 15.2<br>Mortality rates: 18.8% vs 27.0%<br>Nursing home admittance: 26 vs 33 | NA | DET: 1: Missing values were preferably replaced with participants' last available EQ-5D-3L score<br>2: Value of 0 was assigned for deceased persons to assessment time points following dates of death<br>3: Combined the methods used in the first two sensitivity analyses.<br>All showed no significant difference in quality of life between groups at baseline or after 12 or 24 months | Intervention had better outcomes in terms of days in hospital and sense of security in care interaction and a shift to this kind of intervention is possible without increasing costs |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| Ekdahl (2016)[83] | Diseases: blood and blood-forming organs, nervous, circulatory, respiratory, digestive, nutritional, metabolic system, infectious, parasitic, Disorders: mental, behavioural, immune system, and endocrine | USD 71,905 vs 65,626) (USD 102,187.62 vs 93,255.71) | Number of hospitalizations: 2.8 vs 3.4<br>Inpatient days: 15.1 vs 21.0<br>Mortality rates: 25.9% vs 38.5%<br>Nursing home admittance: 30 vs 32 | NA | Not reported | Intervention had better outcomes in terms of survival and days in hospital, while costs not being significantly higher in comparison to usual care |
| Evans (2021)[84f] | Circulatory, respiratory, endocrine, neurological, genitourinary disease, dementia | GBP 6,306 vs 6,334 (USD 7,418.67 vs 7,451.61) | Changes in HRQoL: -0.024<br>Five key symptoms (IPOS-5): -1.20<br>Caregiver burden: -1.80 | Not reported | DET: All three different cost scenarios indicate uncertainty around the cost-effectiveness of intervention: cost of the health + social care service use; cost of the health + social care service use + equipment; cost of the health + social care service use + equipment + informal care | Intervention was cost-effective |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| Gayot (2022)[85] | Heart rhythm disorder, diabetes, neuro-cognitive disorders, depression, COPD, hypertension | Healthcare payer (health insurance perspective): USD -350 (USD -357.25)<br>Healthcare payer (care producer perspective): USD -180 (USD -183.73) | The proportion of patients with unplanned hospitalization: 0.091<br>Number of unplanned hospitalizations: 0.29 vs 0.44<br>Length of hospital stay in days: 9.37 vs 8.14<br>ED admissions: 29 vs 22<br>Consultations by physician: 16.4 vs 15.1<br>Deaths: 40 vs 43<br>HRQoL: 83 vs 77 | Health insurance: USD 3,846 (USD 3,925.82) for each avoided hospitalization<br>Care producer: USD 1,978 (USD 2,019.01) for each avoided hospitalization | Not reported | The intervention significantly reduced unplanned hospitalizations, and the cost-effectiveness of the intervention was not significant at 12 months |
| Lundqvist (2018)[89] | Not reported | EUR 24,678 (USD 43,049.25) | QALYs: 0.54<br>Life years: 1.05 | EUR 45,700 (USD 79,720.83) per QALY gained; EUR 23,502.86 (USD 40,999.29) the cost per life-year gained | DET: When the treatment effect on mortality was set to zero after two years, both the incremental costs QALYs decreased, although the impact on overall cost-effectiveness is small | Intervention was cost-effective if common threshold value for cost-effectiveness of approximately 50,000 EUR per QALY is considered |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| | | | | | PROB: The probability of intervention being cost effective at different threshold values was examined and at a value of 50,000 EUR this probability was approximately 60% | |
| Vila (2015)[93] | AF, COPD, HF, neurologic, osteoarticular disease, dementia, depression, IHD, hematological disease, diabetes, renal failure, cancer, cirrhosis | EUR 17.07 vs 52.70 (USD 29.87 vs 92.21) | Number of hospital admissions: 0.19 vs 0.39<br>Hospital stays in days: 1 vs 3.2<br>ED visits: 0.3 vs 0.2<br>Deaths: 40% of total vs 56% of total<br>EHCs: 0.8 vs 0.7 | NA | Not reported | Intervention reduced the number of hospital admissions and length of stay, and had lower costs |
| **Self-management support interventions** | | | | | | |
| Basu (2015)[81] | Depression and at least one chronic health condition (which is unclear) | USD 350[g] (USD 407.40) | QALYs: 0.007 | USD 50,000 (USD 58,200) per QALY gained[g] | ICER by baseline depression status indicates that it will cost more per QALYs gained for those diagnosed with the disease and it will cost less per QALYs gained for those without it[h] | Intervention was potentially cost-effective |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| Gillespie (2022)[86] | Not reported | EUR -2,548 (USD -3,389.07) | QALYs: 0.031<br>HRQoL:<br>Baseline: 0.44 vs 0.40,<br>Follow-up: 0.51 vs 0.35 | Intervention dominant | DET: The effects of inflating the intervention unit cost inputs by 10% and 50% were examined, alongside putting the cost of intervention at a low value of 182 Euros and the results reflect those from the base case analysis | Intervention was cost-effective |
| Miranda (2022)[91] | Not reported | CAD 1,710 (USD 1,507.61) | QALYs: - 0.03 | Intervention dominated | DET: Intervention would be considered a cost-effective option, if it could improve by at least 0.03 QALYs<br>PROB: Intervention has a 17.3% probability of being cost-effective at the WTP threshold of CAD 50,000/QALY | Intervention was not cost-effective |

| Lead author (publication date) | Conditions with definition of multimorbidity | Incremental cost[a] | Incremental effect[b] | Base case ICER | Sensitivity analysis | Authors' conclusions |
|---|---|---|---|---|---|---|
| Panagioti (2018)[92] | Not reported | GBP 150.58 (USD 253.53) | QALYs: 0.019<br>HRQoL:<br>Baseline: 0.696 vs 0.708, Follow-up: 0.691 vs 0.664<br>Self-management: 1.44<br>WHO quality of life: 1.62<br>Depression: 1.00<br>Self care: - 0.04 | GBP 8,049 (USD 13,343.68) per QALY gained | DET: Complete case analysis showed no change in conclusion; the post hoc sensitivity analysis analyzing costs and outcomes separately in the first six months post baseline (when no intervention was received) confirmed that the period in which participants actually received treatment was driving outcomes, as the effects were restricted to the period in which intervention was delivered | There is over a 70% chance of cost-effectiveness of intervention at conventional levels of WTP |
| **Medicines management interventions** | | | | | | |
| Salari (2022)[95] | Dementia and at least one chronic health condition (which is unclear) | CHF -3,588 (USD -3,158.92) | QALYs: 0.025 | Intervention dominant | DET: Inflating unit costs by 30% showed no change in conclusion<br>PROB: The majority of the bootstrap replications showed no change in conclusion | Intervention was dominant |

AF indicates trial fibrillation; CAD, Canadian Dollar; CHF, Swiss Franc; COPD, chronic obstructive pulmonary disease; DET, deterministic sensitivity analysis; EHC, emergency house call; GBP, Great British Pound; HBCTI, Home-based care transitions intervention; HBP, high blood pressure; HF, heart failure; HRQoL, health-related quality of life; IBS, irritable bowel syndrome; ICER, incremental cost-effectiveness ratio; IHD, ischemic heart disease; ITT, intent to treat; NA, not applicable; NHS, National Health Service; PSS, Personal social services; PROB, probabilistic sensitivity analysis; RA, rheumatoid arthritis; QALYs, quality-adjusted life years; UC, usual care; US, United States; vs, versus; WHO, World Health Organization; WTP, willingness to pay.

[a] Costs reported in original study were converted to 2023 United States Dollar (USD).
[b] Baseline and the last follow-up score are reported for incremental effect when the change in incremental effect is not reported. The last follow-up score is reported when no baseline and change in incremental score are reported.
[c] Negative difference between intervention and usual care groups means that the intervention group health outcomes decreased less than the usual care group health outcomes during the follow-up period.
[d] All outcomes except QALYs assessed at 12 months, negative signs at negative wellbeing, anxiety, and depression, indicate a difference in favour of the interventions group.
[e] Author's interpretations of incremental effects and ICER were incorrect, and misleading. Incremental effect is calculated in a wrong way and authors indicate support for cost-effectiveness but based on a wrongly constructed ICER. In the construction of ICER, the denominator is not a QALY as the authors claim.
[f] This intervention is cost-effective compared to usual care according to the authors; however, the ICER was not reported, and this study has serious limitations in regard to their reporting of the effectiveness of the study. Therefore, the conclusion regarding the cost-effectiveness of this economic evaluation is difficult to reach.
[g] Reported costs are median costs, and base case ICER is median ICER.
[h] This was not reported in the study as sensitivity analysis, but it is reported in this table.

The only care coordination plus support for self-management intervention which was not a CUA was a trial-based CEA from the US, which found that a home-based care transitions intervention was cost-effective, compared to usual care, for most of the groups examined in the study.[94] However, the study results need to be interpreted with caution. The author's interpretations of incremental effects and ICERs were incorrect (and, consequently, misleading).

The remaining care coordination plus self-management support type interventions either did not have conclusive cost-effectiveness results or were not deemed cost-effective by the respective authors. The study from England and Scotland mentioned in the previous paragraph also reported a CCA alongside an RCT and found that intervention involving a multidisciplinary team of nurses, pharmacists, and a physician in comparison to usual care had lower costs from a healthcare sector perspective, but higher when it comes to costs from a limited societal perspective.[96] Regarding health outcomes, QALYs were higher for patients and lower for carers in the intervention compared to the usual care group, and the number of deaths were also higher in the intervention arm. A trial-based CUA from Spain found the integrated healthcare model for patients with multimorbidity (managed by the primary care team, such as general practitioner and nurse with the support of a reference internist and a liaison nurse) was dominated by the usual care comparator.[88] However, the probabilistic sensitivity analysis showed that for the subgroup of people below 80 years old with three or more chronic diseases, the intervention was associated with lower costs in 89% of simulations.

### *Care coordination interventions*

Six economic evaluations[82–85,89,93] reported the cost-effectiveness of care coordination interventions, but the overall cost-effectiveness conclusions are difficult to interpret because half the studies are CCAs. Five out of six care coordination interventions were targeting geriatric multimorbid adults. A CCA alongside an RCT from Sweden found that comprehensive geriatric assessment compared with usual care had higher costs (although not statistically significant) and better health outcomes in terms of the number of days spent in hospital, number of hospitalizations and nursing home admittances, mortality, and sense of security in care interaction.[82] Based on the same group of patients, another trial-based CCA from Sweden reports the cost-effectiveness results the main difference being the longer time horizon in comparison to the previous one (three

years versus two years).[83] This analysis found that comprehensive geriatric assessment compared with patients receiving usual care also had higher costs (although not statistically significant), and better health outcomes regarding the number of days spent in hospital, number of hospitalizations and nursing home admittances, and mortality. A model-based CUA reports the cost-effectiveness results based on the same group of patients as the two above mentioned CCAs from Sweden, the crucial difference being the longer time horizon in comparison to the previous ones (30 years versus three and two years).[89] This analysis found that comprehensive geriatric assessment in comparison with usual care had an ICER of EUR 45,700 (USD 79,720.83) per QALY gained, which is lower than the threshold range of 50,000 EUR per QALY gained often used when considering reimbursement of pharmaceuticals in Sweden.[89] A trial-based CCA from Spain found a home healthcare program compared with usual care had lower costs and better health outcomes in terms of a number of hospital admissions, hospital length of stay, and number of deaths.[93] A CEA alongside an RCT from France found that a preventative geriatric telemedicine assessment program was not cost-effective over a 12-month time horizon.[85]

One care coordination intervention focused on multimorbid adults in palliative care in England. This CEA, conducted alongside an RCT, found a community-based short-term integrated palliative and supportive care intervention in comparison to usual care was cost-effective.[84] However, the ICER was not reported and this study has serious limitations in regards to their reporting of the effectiveness of the study. The conclusion regarding the cost-effectiveness of the intervention is difficult to interpret.

### *Self-management support interventions*

Four economic evaluations[81,86,91,92] reported the cost-effectiveness of self-management support interventions, and the majority (n=3) found these intervention types to be cost-effective. A CUA alongside an RCT from the US found that a chronic disease self-management program, when compared with ‘no intervention’, had an ICER of USD 50,000 (2023: USD 58,200) per QALY gained.[81] In the conclusion of this economic evaluation, it is stated by the authors that although a universally accepted cost-effectiveness threshold does not exist, an ICER of USD 50,000 per QALY gained is considered acceptable, so the intervention is potentially cost-effective for individuals with multimorbidity. A trial-based CUA from Ireland found that an occupational therapy-led

self-management support program is dominant in comparison with usual care.[86] A trial-based CUA from England found that self-management health coaching, when compared with usual care, had an ICER of GBP 8,049 (USD 13,343.68) per QALY gained, which is also lower than the threshold range used by NICE.[92]

The Canadian economic evaluation reported on a self-management support intervention and was found not to be cost-effective in the base case analysis. A model-based CUA found the electronic patient-reported outcome (ePRO) mobile app for self-management is dominated in comparison with usual care.[91] On the other hand, the deterministic sensitivity analysis showed that ePRO would be cost-effective (at the usually used WTP value of CAD 50,000), if the intervention could improve by at least 0.03 QALYs.

### *Medicines management interventions*

One economic evaluation examined an intervention which mainly focused on medicines management but specifically targeted patients with multimorbidity.[95] This trial-based CUA, conducted in Switzerland, Belgium, Ireland, and the Netherlands, found a software-assisted approach to pharmacotherapy optimization, namely the Systematic Tool to Reduce Inappropriate Prescribing, is dominant compared to usual care.[95]

## 2.3.5. Quality assessment of the studies

Quality assessment of the included economic evaluation based on CHEERS 2022 reporting standards are reported in Appendix A.5 and A.6. All economic evaluations met most of the CHEERS reporting standards; however, none met all of the criteria. Fifteen CHEERS checklist items were fulfilled by all economic evaluations. In contrast, health economic analysis plan; discount rate; rationale and description of model; characterize heterogeneity; characterize distributional effects; approach to engagement with patients and others affected by the study; study parameters; and effect of engagement with patients and others affected by the study were the eight items that majority of economic evaluations have not reported or partially reported. An economic evaluation comparing care coordination plus support for self-management intervention, more specifically a home-based care transitions intervention with usual care, which has serious limitations because of incorrect author's interpretations of incremental effects and ICERs, fulfilled

17 out of 28 CHEERS checklist items. An economic evaluation comparing care coordination intervention, more specifically a community-based short-term integrated palliative and supportive care intervention with usual care, which has serious limitations in regard to reporting of the effectiveness, fulfilled 18 out of 28 CHEERS checklist items.

The total quality score of each economic evaluation based on QHES is reported in Appendix A.7. The quality score ranged from 64 to 91 out of 100, with a mean score of 81.7. Overall, 13 out of 17 (76.5%) economic evaluations were considered high quality with a >= 75 score. The quality score of the economic evaluations was also reported based on the type of interventions. Self-management support interventions scored the highest (85.4), followed by care coordination plus self-management support interventions (83.4), and coordinated care interventions (76.7). There was only one study in the medicines management intervention group (score = 87). An economic evaluation comparing care coordination plus support for self-management intervention, more specifically a home-based care transitions intervention with usual care, which has serious limitations because of incorrect author's interpretations of incremental effects and ICERs, had the lowest score of all studies (score = 64). An economic evaluation comparing care coordination intervention, more specifically a community-based short-term integrated palliative and supportive care intervention with usual care, which has serious limitations in regard to reporting of the effectiveness, had the score of 70, well below the average score of all studies.

## 2.4. Discussion

This systematic review identifies and describes the published evidence pertaining to the cost-effectiveness of interventions targeted to people with multimorbidity. The main finding of this review is that there is a great amount of heterogeneity across the studies in terms of how multimorbidity is defined, intervention types, included chronic conditions, types of economic evaluation, examined outcomes, and quality.

The most common definition of multimorbidity described in economic evaluations represents it as having two or more chronic conditions, some do not provide a definition

at all, and only one aligns with the definition this review used which is having two or more chronic conditions where one is not necessarily more important than the other(s). The observation of varied definitions is expected considering that there is no consensus on the definition of multimorbidity globally.[100] It is important to have a clear definition in order to make a comparison between different multimorbidity studies more straightforward.

In this review, 16 studies (17 economic evaluations) were included, which is similar to the number of studies included in the two other reviews (11 in the review by Laberge and colleagues,[65] and 19 in the review by Banstola and colleagues[64] (only one study[81] included in this review was included in the review by Banstola and colleagues)). Despite the more stringent definition of multimorbidity employed in this review, this finding is expected given the fact that the clinical context in this review is broader than in the two other reviews. In the review by Laberge and colleagues,[65] the clinical context was centred on individuals with polypharmacy and in the review by Banstola and colleagues,[64] the clinical context was centred on people with depression. According to the Cochrane Handbook for Systematic Reviews of Interventions, the benefit of a broader clinical scope is a comprehensive summary of evidence.[101] Because of a broader clinical scope in this review, there was a great heterogeneity of chronic conditions observed across the studies, which provided an opportunity to explore findings across different types of participants, that have different types of multimorbidity.

A broader scope of this review in terms of economic evaluation types provided an opportunity to include five CCAs. Because of the difficulties in measuring outcomes in multimorbidity-focused interventions,[24] CCA may be a well suited economic evaluation form in the context of multimorbidity. It is a type of economic evaluation where disaggregated costs and range outcomes are presented, which allows decision-makers to ascribe their values to all outcomes (health and non-health) and costs, and decide on whether to adopt an intervention based on their own values and their own understandings of the results.[61] As seen in the results section of Chapter 2, economic evaluations adopting a CCA form assessed a variety of health (QALYs), and non-health (e.g., participant' sense of security in care, number of deaths, number of hospitalizations) outcomes. Presenting outcomes in a transparent, accessible, and easily understandable way in CCAs,[61] can allow decision-makers to assess measured outcomes in multimorbidity-focused interventions in a more straightforward way.

The broad nature of this review also provided an opportunity to compare the cost-effectiveness of different intervention types.[101] The current evidence lends support to multimorbidity interventions that have a self-management component. However, cost-effectiveness of multimorbidity interventions may be different for patients with different chronic illnesses, considering their complex needs and individual circumstances.[102] Diabetes and depression were the two most common chronic conditions mentioned in the included economic evaluations; however, in general there was a great variety of chronic conditions reported across the studies. The cost-effectiveness results reported in this review should be taken with caution, as the cost-effectiveness implications of multimorbidity interventions are only valid for the types of multimorbidity that have been contextualized by individual studies.[64]

Beyond the finding that most self-management interventions are cost-effective, it is important to reflect on the similarities and differences in economic evaluations that were or were not cost-effective. An important finding from this review is that most economic evaluations deemed cost-effective involved interventions with a medicines management component.[81,86,87,89,94–96] This is significant in the clinical context of multimorbidity due to the fact that patients living with multimorbidity use considerably more prescription medications and have higher prescription drug expenses than individuals living with a single chronic disease.[103] The cost-effective interventions with a medicines management component focused on reducing inappropriate prescribing,[95] and included medicines review to ensure medications are taken as prescribed.[81,86,87,89,94,96] Potential explanations behind interventions with medicines management components being cost-effective is that these interventions likely lead to cost savings by identifying and stopping unnecessary medications (reducing overall medication use) and optimizing dosages.[104–106] Another reason could be that effective medicines management can lead to better control of chronic conditions, resulting in improved health outcomes.[107]

While there is evidence of potentially cost-effective interventions in high-income countries, no study has been found to examine the cost-effectiveness of multimorbidity management in low and middle-income countries. This begs the question as to whether (and to what extent) the high-income countries' evidence of cost-effectiveness in this area would be transferable to low- and middle-income countries'. Determining the true cost-effectiveness of interventions in low- and middle-income countries could be challenging given the fact that the 1-to-3 times gross domestic product (GDP) per capita

threshold, suggested by the WHO, has been severely criticized because it causes more interventions to be recommended as cost-effective.[108,109] Although the WHO has been distancing itself recently from this suggested threshold in low- and middle-income countries,[51,110] a recent review revealed that GDP-based thresholds have been used more frequently in low- and middle-income countries from 2015 to 2020 than from 2000 to 2015 (84.3% versus 66%).[108,111] The recommendation for researchers in low- and middle-income countries is to either include the justification for using 1-to-3 times GDP per capita thresholds or prioritize using local thresholds if they are available.[108]

### 2.4.1. Strengths and limitations

This systematic review has a clear definition of multimorbidity, which was adopted from the paper discussing the future of multimorbidity by Cynthia M. Boyd and Martin Fortin.[3] The advantages of a broad nature of this review are a comprehensive summary of the evidence, an opportunity to explore findings across different types of participants, and a chance to compare the cost-effectiveness of a range of different intervention options.[101] For the reasons mentioned in the Discussion section of Chapter 2, a major strength of this review is including CCAs. Another strength of this review is following the recommendation by Watts and Li that authors of reviews in one subject area should use the same checklist used in previous review(s) in that subject area;[112] therefore, the reporting standards and quality appraisal of the included economic evaluations were evaluated by two checklists, CHEERS 2022 and QHES. The decision to include comorbidity-related terms in the search strategy has made this systematic review more comprehensive given the fact that it has widened the net of potential studies that could be captured.

The review has several limitations. First, grey literature and unpublished economic evaluations were not part of the search strategy. Second, at Stage 2, one paper that could not be accessed through SFU library databases was omitted. Third, since economic evaluations not published in English were excluded, relevant studies may have been missed.

Potential areas of further research relate to geography and patient borne costs. Considering the recent findings showing that South America has the highest prevalence of multimorbidity out of any continent (45.7%),[9] there is a need for interventions and economic evaluations which assess their cost-effectiveness. The majority of costs included in the studies in this review were formal healthcare sector costs, while only the minority of studies examined informal costs. If suitable, future economic evaluations should consider including informal costs, given the fact that informal care constitutes the main cost driver in several chronic conditions such as dementia,[113] coronary heart disease,[114] multiple sclerosis, mental illness, and cancer.[115]

## 2.5. Conclusion

This systematic review provides evidence of a significant heterogeneity across published economic evaluations in the area of multimorbidity. There is great variety in terms of the definition of multimorbidity, intervention types, included chronic conditions, types of economic evaluation, examined outcomes, and quality across the studies. The findings from the systematic review suggest that incorporating medicines management into multimorbidity interventions may be an important driver of cost-effectiveness, due to cost savings and improved health outcomes associated with this component. The identified evidence also suggests that CCA may be a well suited economic evaluation form in the context of multimorbidity, and the following chapter presents a trial-based economic evaluation of a multimorbidity intervention.

# Chapter 3.

# A digital health-based self-management program compared with usual care for patients with multimorbidity: an economic evaluation alongside a randomized controlled trial

## 3.1. Introduction

The preceding chapter provides us with evidence in regard to which types of interventions are cost-effective for people with multimorbidity. It points out that interventions containing *self-management* support component, either as a main or secondary focal point, are likely to be cost-effective options for people with multimorbidity. Chapter 3 reports the findings from a trial-based economic evaluation in the context of a digital health *self-management* program for patients from small urban and rural patients with multimorbidity.

In 2022, Statistics Canada reported that approximately 17.8% of the Canadian population resides in rural regions.[116] Canadians with chronic diseases who live in rural areas have different experiences than their urban counterparts. In rural areas, hospitalizations of chronic illnesses are around 60% higher per capita than in urban areas.[117] In comparison to Canadians who live in urban areas, those who reside in rural areas have a higher prevalence of risk factors that contribute to or exacerbate chronic conditions such as smoking, obesity, and poor nutrition. This inequity between rural and urban Canadians can be explained by the fact that all significant health resources, technologies, expertise, and services are concentrated in urban rather than rural areas. Digital technologies can be effective in helping patients from small urban and rural areas in managing chronic diseases, by giving them the opportunity to get high-quality care within their homes since they would not need to travel extensively to urban areas to receive healthcare.[118]

As discussed in Chapter 1, the limited number of studies examining the effectiveness of DHIs in the context of multimorbidity have shown some promising signs, but there is a paucity of high-quality evidence regarding the cost-effectiveness of such interventions. A

small number of economic evaluations have been conducted to examine the cost-effectiveness of DHIs for people with multimorbidity, and the results are mixed.[85,91,92] A recent economic evaluation from Ontario assessed that the electronic patient-reported outcome (ePRO) mobile app is not cost-effective compared with usual care.[91] However, an economic evaluation from England reported that a telephone health coaching program compared with usual care has a 70% probability to be cost-effective when a QALY is valued at GBP 20,000.[92] A CEA conducted in France determined that a preventative geriatric telemedicine assessment program designed for nursing home residents over 60 years of age with multimorbidity compared with usual care was not cost-effective over a 12-month time horizon.[85]

There are relatively few studies that have examined the cost-effectiveness of DHIs in populations with multimorbidity, and their findings regarding cost-effectiveness are not consistent. These economic evaluations have also not focused on patients from small urban and rural areas, where rates of mortality and hospitalization are higher.[119–121] The study reported in this chapter is an economic evaluation performed alongside an RCT. As described in Chapter 1, the RCT was a two-year follow-up study conducted in primary care settings across small urban and rural areas of BC to assess the effectiveness of the iCDM program compared with usual care for patients with multimorbidity.[122] Using a cost-consequence framework, the objective of the economic evaluation was to explore the cost-effectiveness of the iCDM intervention when compared with usual care.

## 3.2. Methodology

### 3.2.1. Summary details of the RCT

The economic evaluation was driven using primary data from a single-blinded, RCT in patients with multimorbidity.[122] The study received ethics approval from SFU and relevant regional research ethics boards; the registration number for ClinicalTrials.gov is

NCT01342263. The trial protocol was provided in the same paper where the clinical results have been published. Brief details of the RCT are provided below.

### *RCT design*

The primary objective of the RCT was to compare all-cause hospitalizations over a two-year period for patients with two or more chronic illnesses in the iCDM group compared with usual care. The iCDM program did not provide a significant reduction in the number of all-cause hospitalizations among patients with multimorbidity, compared with usual care (relative risk, 0.68; 95% CI, 0.43 to 1.10; p = 0.12). However, patients in the interventions group had fewer admissions to the hospital, fewer deaths, and their time to first hospitalization was longer compared with the usual care group. The iCDM program was provided over two years and consisted of interdependent care which involved interdisciplinary team members: the patient's primary care physician, nurse, exercise specialist, and dietitian. The nurse was administering the iCDM program during standard weekday hours for a patient with the support of an exercise specialist and dietitian. A symptom report encompassing questions about disease-specific symptoms and biometric data (blood pressure level, body weight, and blood glucose level) was reported through the iCDM website by patients daily. If goals for blood pressure level, body weight, and blood glucose level had not been achieved, warnings were activated. The nurse assigned to the patient was emailed regarding warnings and then contacted the patient over the phone within one business day. Referral to the hospital in close proximity, advice for follow-up with the patient's primary care physician, and further assistance in patient self-management were possible interventions implemented after the warning. In addition to the symptom report questions, patients were asked every eight weeks to answer questions regarding their diet, physical activity habits, experience with stress/anxiety/depression, medication adherence and smoking status. For example, the question pertaining to medication adherence was, "*Are you able to take your medications at the correct dose and time more than 80% of the time?*" Special alerts were created if the patient's responses to these questions indicated they would benefit from additional support/counselling. In the case of medication adherence question, additional support would have resulted in general counselling which may include titration of medications. Patients allocated to the usual care group received educational information about chronic illness management and a list of internet-based resources. Except for outcome assessments at 12 and 24 months, no contact between researchers

and patients existed, and patients were able to seek any type of care they wanted during the study.

### *Patients*

The inclusion criteria required that patients were patients in one of 71 primary care clinics in small urban and rural areas throughout BC. Furthermore, patients had to be at least 19 years old, have internet access, and be fluent in English. They also needed to have two or more of the following chronic conditions: diabetes, heart failure (HF), ischemic heart disease (IHD), chronic kidney disease (CKD), or COPD. The targeted recruitment areas were identified as not having ambulatory clinics for the specified chronic diseases in the area at the time of the study. The research team for the clinical trial did this by identifying cities/areas that had them, so they excluded Greater Vancouver, Abbotsford, Kelowna, Victoria, and Nanaimo, leaving the rest of the province which is essentially small urban and rural areas. Patients were randomly assigned on a 1:1 ratio to receive either the iCDM intervention or usual care (details provided above), using variable block sizes. Patients were recruited between October 2011 and March 2015. Of 456 potentially eligible patients, 229 were randomly allocated to receive the iCDM program (n=116) or usual care (n=113).

### *Data collection*

Data collection occurred at baseline, and at 12 months and 24 months post randomization. At baseline, data were collected on medical history (clinic attendance, medications and vitamins used, laboratory tests, and diagnostic tests), smoking status, alcohol consumption, e-health literacy, depression, social demographics, internet use, self-management, and social support. At 12 months, data were collected on hospital, ED, and clinic visits. At 24 months, data were collected on hospital, ED and clinic visits, medications and vitamins received, smoking status, alcohol consumption, laboratory tests, diagnostic tests, self-management, and social support. Health status measures used in the economic evaluation were collected at baseline (EQ-5D-5L and SF-6D), one-year (EQ-5D-5L only), and two-years (EQ-5D-5L and SF-6D) post-randomization. The EQ-5D-5L was included part way through recruitment, after Dr. Whitehurst had joined the study team, which means that baseline EQ-5D-5L data was only available for some of the patients. The description of these instruments will be described later on in this chapter. Data on clinic attendance, smoking status, social demographics, medications,

and vitamins used, laboratory tests, and diagnostic tests were abstracted from the patient's physician's/nurse practitioner's medical record and confirmed by telephone with the patient. For all other outcomes, self-administered questionnaires were mailed to the patient with a stamped return envelope to mail back.

## 3.2.2. Study design and justification for the economic evaluation

The type of economic evaluation performed alongside the RCT is a CCA. As described in Chapter 1, a CCA is a method of economic evaluation which presents outcomes, resource use, and costs in a disaggregated form for all groups under comparison.[36] CADTH recommends that a primary analysis in an economic evaluation should be a CUA; however, a CCA was performed in this economic evaluation. This is because EQ-5D-5L complete data has a small sample size (89 patients), and SF-6D data only has two time points (baseline and 24-month follow-up). Another downside of EQ-5D-5L is that it is based on the group of people who were recruited later in the study. Therefore, early and late recruiters were compared to see if they were similar in terms of characteristics. Also, considering that both health and non-health outcomes were assessed in the RCT, a CCA was a chosen type of design as all outcomes (health and non-health) and costs will be assessed. The difference between health and non-health outcomes has been described in Chapter 1. The cost-consequence approach also allows decision-makers to ascribe their values to health, non-health outcomes and costs, and decide on whether to adopt an iCDM program based on their own understandings of the results.[61]

## 3.2.3. Data collection

### *Healthcare resource use and costs*

Trial patient's use of healthcare resources was collected by self-assessment questionnaires at baseline, and 12 and 24 months post-recruitment (full details of the information collected in the questionnaires is provided in Appendix B.1 (baseline), B.2 (12 months) and B.3 (24 months)). An assessment questionnaire designed by the research team was used to collect resource use data. Information about patients' use of healthcare resources was recorded on hospital, ED, and clinic visits. At the 24-month

follow-up, data was also gathered on medications and vitamins used, laboratory tests, and diagnostic tests. Data on medications and vitamins comprises the dosage, dosage frequency and the name of the medication or vitamin. However, medications, vitamins, laboratory tests, and diagnostic tests were not costed. These resources were not costed because of the way these resource use data were collected. More details on these are provided in the Discussion section. Table 3.1 provides details of all unit costs used in the economic evaluation, and all underlying assumptions (where appropriate). To place a dollar value on the items of healthcare resource use collected from patients, unit costs were obtained from the following sources: the Canadian Institute on Health Information (CIHI)[123,124], BC Medical Services Plan (MSP) payment schedule[125], and a journal article that describes clinic costs[126]. For hospital visits, age-specific full hospital and physician costs per episode of care in BC hospitals are reported. Since the CIHI source on ED visit cost only covers full hospital cost, unit costs for physician cost were obtained from the MSP payment schedule. For clinic visits, an assumption was made that clinics represented outpatient clinics, and unit costs for outpatient clinic visits were used for this service. All unit costs were expressed in CAD at 2022 prices. The Bank of Canada inflation calculator was used to convert non-2022 unit costs to the 2022 equivalent.[127]

**Table 3.1: Unit costs of healthcare resources used in the economic evaluation.**

| Item of resource | Unit cost (CAD)[a] | Details |
|---|---|---|
| **Inpatient services** | | |
| Hospital visit | Episode specific | Age-specific full hospital and physician cost per episode of care[123] |
| **Outpatient services** | | |
| ED visit | 350.68 per visit | Full hospital cost per ED visit[124] |
| MSP for ED visit | Complexity specific | MSP Payment Schedule – 2022 (level 1, 2, and 3 of complexity (level 1 least complex))[125] |
| Clinic visit | 330.78 per visit | Jacobs and Hall[126] |

BC indicates British Columbia; CAD, Canadian Dollar; CIHI, Canadian Institute on Health Information; ED, emergency department; MSP, medical services plan.

[a] Expressed in CAD at 2022 prices.

### *Outcomes*

Secondary outcomes (non-preference-based outcomes) in the RCT consisted of self-management using the Health Education Impact Questionnaire (heiQ),[128] social support

using the Medical Outcomes Study (MOS) Social Support Scale,[115] and quality of life using the 36-item Short Form survey (SF-36).[129]

The heiQ measures eight self-management skills in people with chronic diseases: health directed behaviour; positive and active engagement in life; emotional wellbeing; self-monitoring and insight; constructive attitude shift; skill and technique acquisition; social integration and support; and health service navigation.[130] Scores range from 1-4 within each of the eight skills, with higher scores indicating better self-management, with the exception of the emotional wellbeing dimension, which is reverse scored.[131] The MOS Social Support Survey measures four social support elements: tangible support, emotional support, affectionate support, and positive social interaction, and it has an overall social support index.[132,133] The scores for each item range from 0-100, with higher scores representing greater social support.[134] The SF-36 questionnaire measures the quality of life across eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[135] There are also two summary measures: the physical component summary (PCS) score and the mental component summary (MCS) score.[136] Scores for the PCS and MCS range from 0-100, with higher scores indicating better health.[137] All secondary outcomes were assessed at baseline and 24-month follow-up only.

Two additional outcomes, e-health literacy and depression were assessed, but only at baseline. The e-Health literacy outcome was determined by using the eHealth Literacy Scale (eHEALS), with higher scores (which could range from 8 to 40) indicating greater skills at using online health information to help solve health problems.[138] The 8-item scale is based on a model that differentiates between six literacy skills: traditional literacy, health literacy, information literacy, scientific literacy, computer literacy, and media literacy.[139] Depression was assessed using the Centre for Epidemiologic Studies Depression scale (CES-D), with higher scores (which could range from 0 to 60) indicating greater depression.[140] A CES-D score of 16 or more is used as a cutoff for signalling that an individual is at risk for depression.[141] The CES-D scale contains 20 items, each with four levels of response that refer to the frequency of symptoms.[140]

The preference-based outcome measures collected in the trial were the EQ-5D-5L[142] and SF-6D.[143] The EQ-5D-5L consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[144] Each dimension has five levels of

response: no problems, slight problems, moderate problems, severe problems, and extreme problems. The Canadian value set for the EQ-5D-5L was used to derive health state utilities. 11111 represents the best health state concerning the EQ-5D-5L, and 55555 indicates the worst health state. Using the Canadian value set, EQ-5D-5L index scores can range from -0.148 (the value attached to 55555) to 0.949 (the value attached to 11111). The Canadian scoring function relied on time trade-off valuations.[145]

The SF-6D is a health state classification system that can be derived from two commonly used generic health profile measures, the Short Form 36-item Health Survey (SF-36)[143] or the Short Form 12-item Health Survey (SF-12).[146] In this study, the SF-6D was derived from the SF-36. The SF-6D comprises six dimensions: physical functioning (3 levels), role limitations (4 levels), bodily pain (5 levels), vitality (5 levels), social functioning (5 levels), and mental health (5 levels).[147] Since a Canadian value set of the SF-6D is not available, the UK scoring algorithm was used.[143] The SF-6D index scores range from 0.345 (worst possible health state) to 1.00 (full health).[148] The scoring function was derived using the standard gamble technique.[143]

### 3.2.4. Statistical analysis

Baseline characteristics were compared for individuals in the iCDM and usual care groups. The same baseline characteristics were analyzed and compared for individuals in the iCDM group and usual care groups before and after the addition of EQ-5D-5L as a study outcome. This is because EQ-5D-5L complete data has a small sample size (89 patients), and it is based on the group of people who were recruited later in the study. Therefore, early and late recruiters were compared to see if they were similar in terms of characteristics. The independent samples t-test was used in the analysis of baseline differences for continuous variables, the Chi-squared test was used for nominal variables, while the Kruskal-Wallis test was used for ordered categorical variables.

Following the CADTH guidelines, this CCA takes the perspective of the publicly funded healthcare payer for outcomes and costs.[36] Because this economic evaluation is in the form of CCA, all the outcomes measured in the RCT were included in the analysis, irrespective of whether they were considered health or non-health outcomes. The

primary analysis focused on ‘complete data’ (i.e., data from patients who provided some answers at *every* time point: baseline, 12 months, and 24 months) when reporting disaggregated results for the resource use, costs, and preference-based outcomes. However, the analysis of non-preference-based outcomes and healthcare resources not included in the cost analysis (medications, vitamins, laboratory tests, and diagnostic tests) uses all observed data (i.e., data from patients who provided some answers at *any* time point: baseline, 12 months, and 24 months). Between-group change scores with regard to non-preference-based health outcomes were calculated by subtracting the follow-up scores (i.e., the 24-month scores) from the baseline scores. Change scores were then compared between groups using an independent samples t-test. Outcomes data were analyzed by reporting disaggregated means and standard deviations at each time point (for both groups).

In the cost analysis, only costs and resource use items that align with the publicly funded healthcare perspective (i.e., hospital, ED, and clinic visits) are presented in a disaggregated form. The costing of each individual item of resource use was conducted by multiplying the number of units of each resource used by the respective unit cost (as reported in Table 3.1). Disaggregated means and standard deviations were reported for resource use, and cost data for three time periods (baseline to 12 months, 12 to 24 months, and baseline to 24 months). The mean difference between groups for both costs and outcomes were calculated by subtracting the mean scores of the iCDM group from those in the usual care group. Regarding medications and vitamins, these data were organized by therapeutic category (the pathology they are intended to treat) following the United States Pharmacopeia (USP) 2022 drug classification.[149] Patients’ responses to the EQ-5D-5L were converted to health state utilities using the Canadian value set.[145] The QALYs were generated by multiplying health state values with the amount of time spent in each state, and these results were summed to make the total number of QALYs.[55] Health state utilities for the SF-6D were acquired from the SF-36, using the UK the scoring algorithm.[143] The imbalance between intervention and control group mean differential QALYs was controlled by using a multiple linear regression. A p-value of 0.05 was used as the significance level for all analyses. Given the 24-month follow-up period of the RCT, discounting of costs and health outcomes, occurring beyond one year, was done at a rate of 1.5% per year.[36] All statistical analyses were performed with SPSS for Windows 10 (version 27) and Microsoft Excel (version 2016).

### 3.2.5. Sensitivity analysis

Sensitivity analysis was conducted to assess the robustness of study findings to the unit costs of hospital visits. In the base case analysis, age-specific full hospital and physician costs per episode of care in BC hospitals were used. In the sensitivity analysis, non-age specific full hospital and physician costs per episode of care in BC hospitals were used.

## 3.3. Results

### 3.3.1. Participants and baseline characteristics

Overall, 229 patients participated at baseline, 220 (96.1%) at 12 months, and 210 (91.7%) at 24 months. All 210 participants at the 24-month follow-up period participated at 12 months. This means that, in total, 210 patients participated at all three time points, with 19 lost to follow-up (i.e., 19 people did not participate at one or both of the follow-up stages). It is important to point out that 'participation' does not necessarily mean that respondents provided answers to every question in the respective questionnaire. Appendix B.4 provides a comparison of baseline characteristics for patients lost to follow-up (n=19) and those who remained in the study throughout (n=210). Statistically significant differences were observed, with those lost to follow-up having a higher number of chronic diseases ($p = 0.021$), higher alcohol consumption ($p = 0.003$), and more likely to report having chronic heart failure ($p < 0.001$). Of the 19 participants lost to follow-up, 17 were because of death. There was no statistically significant difference in the number of deaths between the iCDM group (n=8) and the control group (n=9) ($p = 0.759$). Additionally, nine patients died during the first year of follow-up, while eight patients died during the second year of follow-up. In the analysis, death was treated as a 'loss to follow-up', the same as if an individual withdrew from the study or if a participant could not be contacted. Table 3.2 provides the baseline characteristics of patients. The mean age of patients was 70.5 years, and the majority (61.6%) were male. Regarding the type of chronic disease, the majority of patients had diabetes (71.6%), with ischemic heart disease being the second most common illness (59.0%). The majority of patients in both groups were retired, married, had a high school or equivalent, and used the internet on daily a basis.

**Table 3.2: Baseline characteristics of patients. Values are numbers (percentages) unless stated otherwise.[a]**

| Characteristic | All participants (n=229) | iCDM (n=116) | Usual care (n=113) | *p* value[b] |
|---|---|---|---|---|
| Age, mean (sd) | 70.5 (9.1) | 69.6 (8.8) | 71.3 (9.5) | 0.164 |
| Sex | | | | |
| Female | 88 (38.4) | 44 (37.9) | 44 (38.9) | 0.876 |
| Male | 141 (61.6) | 72 (62.1) | 69 (61.1) | |
| Chronic disease | | | | |
| Ischemic heart disease | 135 (59.0) | 69 (59.5) | 66 (58.4) | 0.869 |
| Chronic heart failure | 50 (21.8) | 25 (21.6) | 25 (22.1) | 0.917 |
| Diabetes | 164 (71.6) | 84 (72.4) | 80 (70.8) | 0.786 |
| Chronic kidney disease | 133 (58.1) | 62 (53.4) | 71 (62.8) | 0.150 |
| COPD | 70 (30.6) | 37 (31.9) | 33 (29.2) | 0.658 |
| No. of chronic diseases, mean (sd) | 2.41 (0.6) | 2.39 (0.6) | 2.43 (0.7) | 0.594 |
| Educational level | | | | |
| Did not finish high school | 42 (18.3) | 20 (17.2) | 22 (19.5) | 0.268 |
| High school or equivalent | 68 (29.7) | 33 (28.4) | 35 (31.0) | |
| Some post-secondary education | 53 (23.1) | 25 (21.6) | 28 (24.8) | |
| Post-secondary degree | 50 (21.8) | 28 (24.1) | 22 (19.5) | |
| Postgraduate degree | 11 (4.8) | 6 (5.2) | 5 (4.4) | |
| Other[c] | 5 (2.2) | 4 (3.4) | 1 (0.9) | |
| Pre-tax household income | | | | |
| Less than $20,000 | 30 (13.1) | 14 (12.1) | 16 (14.2) | 0.002 |
| $20,000 to $29,999 | 42 (18.3) | 18 (15.5) | 24 (21.2) | |
| $30,000 to $39,999 | 36 (15.7) | 12 (10.3) | 24 (21.2) | |
| $40,000 to $49,999 | 29 (12.7) | 10 (8.6) | 19 (16.8) | |
| $50,000 to $60,000 | 27 (11.8) | 18 (15.5) | 9 (8.0) | |
| More than $60,000 | 59 (25.8) | 40 (34.5) | 19 (16.8) | |
| Current employment status | | | | |
| Full-time job | 22 (9.6) | 11 (9.5) | 11 (9.7) | 0.128 |
| Part-time job | 6 (2.6) | 4 (3.4) | 2 (1.8) | |
| Unemployed | 6 (2.6) | 3 (2.6) | 3 (2.7) | |
| Retired | 173 (75.5) | 91 (78.4) | 82 (72.6) | |
| Other[c] | 21 (9.2) | 16 (13.8) | 5 (4.4) | |
| Marital status | | | | |
| Single | 12 (5.2) | 4 (3.4) | 8 (7.1) | |

| Characteristic | All participants (n=229) | iCDM (n=116) | Usual care (n=113) | *p* value[b] |
|---|---|---|---|---|
| Married | 153 (66.8) | 80 (69.0) | 73 (64.6) | |
| Divorced | 17 (7.4) | 11 (9.5) | 6 (5.3) | |
| Widowed | 34 (14.8) | 19 (16.4) | 15 (13.3) | 0.303 |
| Common law | 8 (3.5) | 5 (4.3) | 3 (2.7) | |
| Other[c] | 5 (2.2) | 1 (0.9) | 4 (3.5) | |
| Frequency of internet usage | | | | |
| Daily | 166 (72.5) | 88 (75.9) | 78 (69.0) | |
| More than once a week | 23 (10.0) | 9 (7.8) | 14 (12.4) | |
| Once a week | 18 (7.9) | 8 (6.9) | 10 (8.8) | 0.305 |
| Once a month | 5 (2.2) | 3 (2.6) | 2 (1.8) | |
| Never | 17 (7.4) | 8 (6.9) | 9 (8.0) | |
| e-Health literacy, mean (sd) | 31.0 (8.4) | 30.5 (7.9) | 31.6 (9.0) | 0.332 |
| Depression, mean (sd) | 12.3 (10.8) | 11.2 (9.8) | 13.4 (11.6) | 0.123 |
| Smoking status | | | | |
| Current | 19 (8.3) | 8 (7.0) | 11 (9.9) | |
| Former | 146 (63.8) | 72 (63.2) | 74 (66.7) | 0.466 |
| Never | 60 (26.2) | 34 (29.8) | 26 (23.4) | |
| Alcohol consumption | | | | |
| never/<1 per week | 133 (58.1) | 67 (57.8) | 66 (58.4) | |
| 1-5 per week | 54 (23.6) | 26 (22.4) | 28 (24.8) | 0.857 |
| 6-10 per week | 26 (11.4) | 16 (13.8) | 10 (8.8) | |
| >10 per week | 16 (7.0) | 7 (6.0) | 9 (8.0) | |

CES-D indicates Centre for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; eHEALS, eHealth Literacy Scale; iCDM, internet chronic disease management; n, number; No., number.

[a] With the exception of the 'Chronic disease' question (where an inclusion criterion was for patients to have two or more of the listed chronic diseases), all questions had mutually-exclusive response options. Numbers do not always sum to the respective totals because of missing data.
[b] Details of the statistical tests used for the different variables (continuous, nominal, and categorical) are provided on page 64. P values are reported to three decimal places.
[c] 'Other' comprises responses that could not be categorized in one of the response options listed in the baseline assessment questionnaire.

Patients in the usual care group had a greater eHEALS score at baseline, compared with patients in the iCDM group (31.6 versus 30.5). Both groups scored below 16 on the CES-D, which indicates that, on average, both groups are not at risk for depression. The only statistically significant difference between the intervention and control group at baseline was the distribution of responses across the income categories (p = 0.002). A

comparison of baseline characteristics for patients recruited before and after the addition of the EQ-5D-5L is also provided in Appendix B.5. As can be seen, there is no significant difference when considering the majority of characteristics. However, there is a statistically significant association between timing of recruitment and educational level (p = 0.005). As mentioned in the Methodology section, determining whether patients have similar baseline characteristics was needed because EQ-5D-5L complete data has a small sample size (89 patients) and it relies on the group of people who were recruited later in the study.

### 3.3.2. Healthcare resource use and costs

Disaggregated estimates of mean resource use for patients with complete data are presented in Table 3.3 for the following time periods: baseline to 12 months, 12 months to 24 months, and baseline to 24 months. The equivalent resource use analysis for the observed data set is provided in Appendix B.6. Corresponding mean healthcare costs are shown in Table 3.4. The equivalent healthcare cost analysis for the observed data set is presented in Appendix B.7. During the baseline to 12-month follow-up period, total costs per patient in the usual care group were higher than those in the iCDM program but it was not statistically significant (mean difference -$718.48, p = 0.728, 95% CI, -$4789.83 to $3352.87). No statistically significant differences in healthcare costs were observed between baseline and 12 months for any of the resource use items. Total costs per patient in the usual care group were also higher than those in the iCDM group for the 12-month-to-24-month period, although the difference was not statistically significant (mean difference -$1629.14, p = 0.284, 95% CI, -$4616.27 to $1357.99). There were no statistically significant differences in healthcare costs between 12 and 24 months for any of the resource use items. Total healthcare costs were higher in the usual care group for all three study periods, although none of the differences were statistically significant (Table 3.3). Table 3.3 also shows that there were no statistically significant differences between groups for any of the individual resource use. Over the full follow-up period, a resource use item that was the main driver of the total healthcare cost estimates was inpatient visits to the hospital (iCDM = $8615.57 and usual care = $11804.09).

**Table 3.3: Resource use per patient over 24 months, by treatment group. Values are mean (standard deviation) number of visits for complete cases unless otherwise stated.**

| Item of resource | iCDM (n=106) | Usual care (n=104) |
|---|---|---|
| **B to 12M** | | |
| *Inpatient services* | | |
| Hospital visit | 0.42 (0.85) | 0.42 (0.83) |
| *Outpatient services* | | |
| ED visit | 0.37 (0.73) | 0.48 (0.90) |
| Clinic visit | 3.19 (18.52) | 0.22 (0.88) |
| **12M to 24M** | | |
| *Inpatient services* | | |
| Hospital visit | 0.41 (0.95) | 0.45 (0.80) |
| *Outpatient services* | | |
| ED visit | 0.49 (1.11) | 0.36 (0.70) |
| Clinic visit | 0.63 (3.27) | 0.90 (4.06) |
| **B to 24M** | | |
| *Inpatient services* | | |
| Hospital visit | 0.82 (1.45) | 0.88 (1.32) |
| *Outpatient services* | | |
| ED visit | 0.86 (1.48) | 0.84 (1.34) |
| Clinic visit | 3.82 (18.71) | 1.13 (4.18) |

B indicates baseline; ED, emergency department; iCDM, internet chronic disease management; M, months; n, number.

Appendix B.8 shows the analysis of healthcare resources not included in the cost analysis (medications and vitamins used, laboratory tests, and diagnostic tests performed per patient at baseline and 24 months). When comparing the two groups, only two statistically significant findings were observed at baseline: the mean number of chest x-ray diagnostic tests performed, and the mean number of antidepressants consumed per patient.

**Table 3.4: Healthcare costs ($) per patient over 24 months, by treatment group, for the complete case data set. Values are mean (standard deviation) costs ($) unless stated otherwise.**

| Item of resource | iCDM (n=106) | Usual care (n=104) | Mean difference[a] (95% CI; p value) |
|---|---|---|---|
| **B to 12M** | | | |
| *Inpatient services* | | | |
| Hospital visit | 4629.16 (9478.40) | 6274.06 (18001.63) | -1644.91 (-5548.55 to 2258.73; 0.407) |
| *Outpatient services* | | | |
| ED visit | 129.02 (257.58) | 171.97 (316.67) | -42.94 (-121.41 to 35.52; 0.282) |
| MSP for ED visit | 33.29 (70.60) | 45.52 (93.08) | -12.22 (-34.67 to 10.22; 0.284) |
| Clinic | 1054.75 (6125.21) | 73.15 (291.36) | 981.60 (-203.87 to 2167.06; 0.104) |
| Total costs | 5846.22 (11101.95) | 6564.70 (18068.72) | -718.48 (-4789.83 to 3352.87; 0.728) |
| **12M to 24M** | | | |
| *Inpatient services* | | | |
| Hospital visit | 4106.90 (10329.45) | 5697.17 (11200.58) | -1427.79 (-4520.65 to 1340.11; 0.286) |
| *Outpatient services* | | | |
| ED visit | 172.03 (387.93) | 128.13 (244.61) | 43.90 (-44.52 to 132.32; 0.329) |
| MSP for ED visit | 36.82 (85.62) | 29.69 (61.86) | 7.13 (-13.23 to 27.48; 0.491) |
| Clinic | 209.08 (1082.56) | 298.97 (1334.24) | -89.90 (-421.63 to 241.84; 0.594) |
| Total costs | 4524.83 (10444.60) | 6153.96 (11496.71) | -1629.14 (-4616.27 to 1357.99; 0.284) |
| **B to 24M** | | | |

| Item of resource | iCDM (n=106) | Usual care (n=104) | Mean difference[a] (95% CI; p value) |
|---|---|---|---|
| *Inpatient services* | | | |
| Hospital visit | 8615..57 (15117.36) | 11804.09 (23163.20) | -3336.28 (-8862.48 to 1442.75; 0.157) |
| *Outpatient services* | | | |
| ED visit | 296.01 (510.03) | 296.34 (464.16) | -0.33 (-133.08 to 132.41; 0.996) |
| MSP for ED visit | 69.03 (124.70) | 74.33 (123.40) | -5.31 (-39.06 to 28.45; 0.757) |
| Clinic | 1257.69 (6185.72) | 363.36 (1344.79) | 894.34 (-328.92 to 2117.59; 0.151) |
| Total costs | 10238.30 (16111.01) | 12538.12 (23469.05) | -2447.58 (-8150.84 to 2449.52; 0.290) |

B indicates baseline; ED, emergency department; iCDM, internet chronic disease management; MSP, medical services plan; M, months; n, number.

[a] Differences in mean values were calculated as values for patients receiving iCDM minus values for patients receiving usual care.

### 3.3.3. Outcomes

Table 3.5 reports results for the non-preference-based outcomes, for observed cases, at baseline and 24 months, by treatment group. Change scores were also calculated for the intervention group and control group. Significant differences were found for one of the five MOS domains: emotional and informational support in iCDM intervention (mean = 2.51) significantly differed from usual care (mean = -0.13) on their pre-post change scores, p = 0.008. Significant differences were found for two of the eight heiQ domains: skill and technique acquisition in iCDM intervention (mean = 0.23) significantly differed from usual care (mean = -0.12) on their pre-post change scores, p = 0.006; emotional wellbeing in iCDM intervention (mean = 0.18) significantly differed from usual care (mean = -0.09) on their pre-post change scores, p = 0.030. Significant difference was found for one of the eight SF-36 domains: emotional wellbeing in iCDM intervention (mean = 2.88) significantly differed from usual care (mean = -1.09) on their pre-post change scores, p = 0.039.

Table 3.6 presents results for the preference-based outcomes (index scores and discounted QALY estimates) over 24 months, by treatment group. Looking at the complete data, the EQ-5D-5L index scores and discounted QALYs were consistently higher for those in the usual care group compared with those in the intervention group, but the differences were not statistically significant. The EQ-5D-5L incremental QALY estimate after controlling for baseline health state values was also in favour of usual care, although the difference was not significant (mean difference -0.028, 95 % CI, -0.08 to 0.03, p = 0.308). SF-6D index scores at 24-month follow-up and discounted QALYs were higher for those in the iCDM group compared with those in the usual care group, but the differences were not statistically significant. The SF-6D incremental QALY estimate, after controlling for baseline health state values, was also in favour of the iCDM intervention. Here, the difference was statistically significant (mean difference 0.037, 95 % CI, 0.00 to 0.07, p = 0.046).

**Table 3.5: Non-preference-based outcomes for observed cases over 24 months, by treatment group.**

| Outcome | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| **MOS** | | | | | |
| Emotional and informational support B | 116 | 29.00 (8.54) | 111 | 29.69 (8.76) | -0.694 (-2.96 to 1.57; 0.546) |
| Emotional and informational support 24 months | 101 | 31.06 (7.82) | 98 | 29.85 (8.48) | 1.212 (-1.07 to 3.49; 0.295) |
| Emotional and informational support change score[b] | 101 | 2.51 (6.97) | 98 | -0.13 (6.92) | 2.648 (0.70 to 4.59; 0.008) |
| Tangible support B | 116 | 16.36 (4.36) | 111 | 15.59 (4.97) | 0.776 (-0.45 to 2.00; 0.212) |
| Tangible support 24 months | 101 | 16.93 (4.09) | 98 | 15.89 (4.43) | 1.043 (-0.15 to 2.23; 0.086) |
| Tangible support change score[b] | 101 | 0.82 (3.80) | 98 | 0.27 (3.86) | 0.556 (-0.51 to 1.63; 0.307) |
| Affectionate support B | 116 | 13.06 (3.26) | 111 | 12.36 (3.33) | 0.700 (-0.16 to 1.56; 0.111) |
| Affectionate support 24 months | 101 | 13.17 (2.90) | 98 | 12.66 (3.13) | 0.505 (-0.36 to 1.32; 0.239) |
| Affectionate support change score[b] | 101 | 0.20 (2.29) | 98 | 0.11 (2.10) | 0.086 (-0.53 to 0.70; 0.783) |
| Positive social interaction B | 116 | 12.41 (3.10) | 111 | 11.60 (3.58) | 0.802 (-0.07 to 1.68; 0.073) |
| Positive social interaction 24 months | 101 | 12.24 (3.18) | 98 | 11.88 (3.38) | 0.360 (-0.34 to 1.35; 0.440) |
| Positive social interaction change score[b] | 101 | -0.03 (2.92) | 98 | 0.00 (2.60) | -0.030 (-0.80 to 0.74; 0.940) |
| Overall support index B | 116 | 74.81 (17.33) | 111 | 72.99 (19.70) | 1.819 (-3.03 to 6.67; 0.460) |
| Overall support index 24 months | 101 | 77.37 (16.66) | 98 | 74.19 (18.01) | 3.172 (-1.68 to 8.02; 0.198) |
| Overall support index change score[b] | 101 | 3.55 (13.15) | 98 | 0.32 (12.97) | 3.238 (-0.42 to 6.89; 0.082) |
| **heiQ** | | | | | |
| Positive and active engagement B | 116 | 4.92 (0.88) | 111 | 4.56 (1.09) | 0.359 (0.10 to 0.62; 0.007) |
| Positive and active engagement 24 months | 100 | 4.86 (0.83) | 96 | 4.39 (1.10) | 0.470 (0.10 to 0.62; 0.001) |
| Positive and active engagement change score[b] | 100 | -0.08 (0.84) | 96 | -0.25 (0.91) | 0.176 (-0.07 to 0.42; 0.159) |
| Health directed behaviour B | 116 | 4.07 (1.44) | 111 | 3.90 (1.47) | 0.180 (-0.20 to 0.56; 0.352) |

| Outcome | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| Health directed behaviour 24 months | 100 | 4.40 (1.27) | 96 | 3.84 (1.38) | 0.551 (0.18 to 0.92; 0.004) |
| Health directed behaviour change score[b] | 100 | 0.24 (1.17) | 96 | -0.02 (1.43) | 0.263 (-0.10 to 0.63; 0.160) |
| Skill and technique acquisition B | 116 | 4.59 (0.78) | 111 | 4.56 (0.85) | 0.031 (-0.18 to 0.24; 0.773) |
| Skill and technique acquisition 24 months | 100 | 4.78 (0.80) | 96 | 4.48 (0.86) | 0.303 (0.07 to 0.54; 0.012) |
| Skill and technique acquisition change score[b] | 100 | 0.23 (0.91) | 96 | -0.12 (0.82) | 0.345 (0.10 to 0.59; 0.006) |
| Constructive attitude shift B | 116 | 5.16 (0.65) | 111 | 4.93 (0.85) | 0.231 (0.03 to 0.43; 0.023) |
| Constructive attitude shift 24 months | 100 | 5.18 (0.68) | 96 | 4.88 (0.87) | 0.299 (0.08 to 0.52; 0.008) |
| Constructive attitude shift change score[b] | 100 | 0.03 (0.73) | 96 | -0.09 (0.77) | 0.124 (-0.09 to 0.34; 0.250) |
| Self-monitoring & insight B | 116 | 5.03 (0.59) | 111 | 4.95 (0.66) | 0.084 (-0.08 to 0.25; 0.310) |
| Self-monitoring & insight 24 months | 100 | 5.18 (0.60) | 96 | 5.02 (0.58) | 0.161 (-0.01 to 0.33; 0.057) |
| Self-monitoring & insight change score[b] | 100 | 0.20 (0.66) | 96 | 0.07 (0.53) | 0.130 (-0.04 to 0.30; 0.132) |
| Health services navigation B | 116 | 5.21 (0.67) | 111 | 5.11 (0.79) | 0.102 (-0.10 to 0.29; 0.291) |
| Health services navigation 24 months | 100 | 5.22 (0.82) | 96 | 5.17 (0.80) | 0.055 (-0.17 to 0.28; 0.633) |
| Health services navigation change score[b] | 100 | 0.07 (0.71) | 96 | 0.01 (0.72) | 0.062 (-0.14 to 0.26; 0.545) |
| Social integration & support B | 116 | 4.71 (1.00) | 111 | 4.57 (1.14) | 0.143 (-0.14 to 0.42; 0.317) |
| Social integration & support 24 months | 100 | 4.84 (0.94) | 96 | 4.51 (1.22) | 0.324 (0.02 to 0.63; 0.038) |
| Social integration & support change score[b] | 100 | 0.21 (0.79) | 96 | -0.05 (1.04) | 0.254 (-0.01 to 0.51; 0.055) |
| EWB B | 116 | 4.73 (1.05) | 111 | 4.46 (1.21) | 0.265 (-0.03 to 0.56; 0.079) |
| EWB 24 months | 100 | 4.87 (1.02) | 96 | 4.43 (1.17) | 0.439 (0.13 to 0.75; 0.006) |
| EWB change score[b] | 100 | 0.18 (0.87) | 96 | -0.09 (0.88) | 0.273 (0.03 to 0.52; 0.030) |
| **SF-36** | | | | | |
| PF B | 116 | 60.17 (28.09) | 113 | 54.91 (26.12) | 5.261 (-1.81 to 12.33; 0.144) |

| Outcome | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| PF 24 months | 100 | 60.85 (27.04) | 99 | 49.34 (27.73) | 11.507 (3.85 to 19.16; 0.003) |
| PF change score[b] | 100 | -1.30 (21.61) | 99 | -5.81 (21.05) | 4.508 (-1.46 to 10.47; 0.138) |
| RF/physical B | 116 | 51.72 (41.41) | 113 | 40.27 (40.97) | 11.459 (0.73 to 22.19; 0.036) |
| RF/physical 24 months | 100 | 48.75 (41.04) | 99 | 41.92 (42.98) | 6.831 (-4.92 to 18.58; 0.253) |
| RF/physical change score[b] | 100 | -3.25 (38.21) | 99 | 0.76 (42.02) | -4.008 (-15.23 to 7.22; 0.482) |
| RF/emotional B | 116 | 75.57 (35.54) | 113 | 70.21 (39.43) | 5.367 (-4.40 to 15.14; 0.280) |
| RF/emotional 24 months | 100 | 78.33 (34.29) | 99 | 68.01 (43.36) | 10.320 (-0.60 to 21.24; 0.064) |
| RF/emotional change score[b] | 100 | 4.00 (44.27) | 99 | -2.69 (42.78) | 6.695 (-5.48 to 18.87; 0.279) |
| Energy/fatigue B | 116 | 55.43 (22.50) | 113 | 51.11 (19.48) | 4.325 (-1.16 to 9.81; 0.122) |
| Energy/fatigue 24 months | 100 | 56.65 (20.79) | 99 | 52.37 (21.33) | 4.276 (-1.61 to 10.16; 0.154) |
| Energy/fatigue change score[b] | 100 | 1.50 (18.98) | 99 | -0.76 (14.52) | 2.258 (-2.47 to 6.99; 0.348) |
| EWB B | 116 | 77.79 (14.30) | 113 | 75.79 (19.17) | 2.005 (-2.39 to 6.40; 0.370) |
| EWB 24 months | 100 | 80.24 (14.53) | 99 | 75.72 (19.35) | 4.523 (-0.26 to 9.30; 0.064) |
| EWB change score[b] | 100 | 2.88 (14.12) | 99 | -1.09 (12.74) | 3.971 (0.21 to 7.73; 0.039) |
| SF B | 116 | 77.59 (22.39) | 113 | 71.57 (27.00) | 6.015 (-0.44 to 12.47; 0.067) |
| SF 24 months | 100 | 77.25 (25.34) | 99 | 69.19 (26.63) | 8.058 (0.79 to 15.32; 0.030) |
| SF change score[b] | 100 | -0.25 (25.19) | 99 | -3.41 (20.58) | 3.159 (-3.27 to 9.59; 0.334) |
| Pain B | 116 | 63.19 (24.89) | 113 | 57.81 (25.96) | 5.380 (-1.59 to 12.35; 0.129) |
| Pain 24 months | 100 | 62.20 (29.09) | 99 | 57.42 (27.65) | 4.776 (-3.16 to 12.71; 0.237) |
| Pain change score[b] | 100 | -0.05 (24.37) | 99 | -0.83 (22.19) | 0.783 (-5.73 to 7.30; 0.813) |
| General Health B | 116 | 55.30 (21.46) | 113 | 50.58 (23.01) | 4.727 (-1.07 to 10.52; 0.109) |
| General Health 24 months | 100 | 55.90 (22.19) | 99 | 51.52 (21.30) | 4.385 (-1.70 to 10.47; 0.157) |

| Outcome | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| General Health change score[b] | 100 | 0.25 (17.41) | 99 | -1.11 (15.67) | 1.361 (-3.27 to 5.99; 0.563) |
| PCS B | 116 | 38.59 (11.62) | 113 | 35.63 (11.56) | 2.956 (-0.06 to 5.97; 0.055) |
| PCS 24 months | 100 | 37.73 (12.34) | 99 | 35.00 (11.69) | 2.729 (-0.62 to 6.08; 0.110) |
| PCS change score[b] | 100 | -1.11 (8.18) | 99 | -0.96 (9.40) | -0.162 (-2.63 to 2.30; 0.897) |
| MCS B | 116 | 52.77 (8.95) | 113 | 51.51 (10.45) | 1.267 (-1.27 to 3.80; 0.325) |
| MCS 24 months | 100 | 53.61 (9.36) | 99 | 51.55 (11.57) | 2.060 (-0.87 to 4.99; 0.167) |
| MCS change score[b] | 100 | 1.69 (9.69) | 99 | -0.56 (9.29) | 2.249 (-0.41 to 4.90; 0.096) |

B indicates baseline; CI, confidence interval; heiQ, health education impact questionnaire; EWB, emotional wellbeing; iCDM, internet chronic disease management; MCS, Mental Component Summary Score; PCS, Physical Component Summary Score; PF, physical functioning; RF, role functioning; n, number; sd, standard deviation; SF, social functioning.

[a] Mean difference calculated as the intervention group (iCDM) estimate minus the control group (usual care) estimate.

[b] Differences in the change between the groups tested using an independent samples t-test.

**Table 3.6: Preference-based outcomes (index scores and discounted QALY estimates) over 24 months, by treatment group.**

| Outcome | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| **EQ-5D-5L** | | | | | |
| *Observed data* | | | | | |
| Baseline | 59 | 0.781 (0.17) | 50 | 0.773 (0.18) | 0.007 (-0.06 to 0.07; 0.825) |
| 12-month follow-up | 86 | 0.763 (0.17) | 83 | 0.767 (0.19) | -0.004 (-0.06 to 0.05; 0.888) |
| 24-month follow-up | 101 | 0.785 (0.17) | 99 | 0.736 (0.19) | 0.049 (-0.00 to 0.10; 0.055) |
| *Complete data*[b] | | | | | |
| Baseline | 45 | 0.775 (0.18) | 44 | 0.777 (0.19) | -0.002 (-0.08 to 0.07; 0.960) |
| 12-month follow-up | 45 | 0.763 (0.16) | 44 | 0.785 (0.16) | -0.022 (-0.09 to 0.04; 0.501) |
| 24-month follow-up | 45 | 0.763 (0.19) | 44 | 0.779 (0.16) | -0.016 (-0.09 to 0.06; 0.672) |
| QALYs | 45 | 1.488 (0.29) | 44 | 1.519 (0.30) | -0.031 (-0.16 to 0.09; 0.620) |
| QALYs (cont.)[c] | - | - | - | - | -0.028 (-0.08 to 0.03; 0.308) |
| **SF-6D** | | | | | |
| *Observed data* | | | | | |
| Baseline | 115 | 0.670 (0.12) | 113 | 0.682 (0.11) | -0.013 (-0.04 to 0.02; 0.421) |
| 24-month follow-up | 100 | 0.699 (0.13) | 98 | 0.664 (0.13) | 0.035 (-0.00 to 0.07; 0.064) |
| *Complete data*[b] | | | | | |
| Baseline | 99 | 0.670 (0.12) | 98 | 0.677 (0.11) | -0.007 (-0.04 to 0.03; 0.675) |
| 24-month follow-up | 99 | 0.700 (0.13) | 98 | 0.664 (0.13) | 0.037 (-0.00 to 0.07; 0.052) |
| QALYs | 99 | 1.332 (0.18) | 98 | 1.302 (0.16) | 0.030 (-0.02 to 0.08; 0.216) |
| QALYs (cont.)[c] | - | - | - | - | 0.037 (0.00 to 0.07; 0.046) |

CI indicates confidence interval; cont., controlled; iCDM, internet chronic disease management; n, number; QALY, quality-adjusted life year; sd, standard deviation.

[a] Mean difference calculated as the intervention group (iCDM) estimate minus the control group (usual care) estimate.
[b] 'Complete data' samples include respondents providing responses to the respective outcome measures at all timepoints (i.e., baseline, 12 months and 24 months for the EQ-5D-5L; baseline and 24 months for the SF-6D).
[c] Incremental QALY estimate after controlling for baseline health state valuations.

### 3.3.4. Further (unplanned) analysis of the SF-6D

The findings presented in Table 3.6 led us to conduct further exploratory analysis, with a view to developing a better understanding of the reasons behind EQ-5D-5L results favouring usual care and SF-6D results favouring the iCDM program. Table 3.7 provides

SF-6D results (index scores and discounted QALYs) over 24 months, by treatment group, for two subgroups: (i) patients recruited before the addition of the EQ-5D-5L as a study outcome ('early' recruitment) and (ii) patients recruited after the addition of the EQ-5D-5L as a study outcome ('late' recruitment). If these two groups were systematically different from each other, this could explain the HRQol differences. The results in Table 3.7 show that the mean HRQoL in the two groups ('early recruiters' and 'late recruiters') is different.

**Table 3.7: Further (unplanned) analysis of the SF-6D (index scores and discounted QALYs) over 24 months, by treatment group, for patients recruited before and after the addition of the EQ-5D-5L as a study outcome.**

| SF-6D outcome | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| **Early recruitment** | | | | | |
| *Observed data* | | | | | |
| Baseline | 56 | 0.681 (0.11) | 63 | 0.721 (0.09) | -0.040 (-0.08 to -0.00; 0.031) |
| 24-month follow-up | 54 | 0.707 (0.13) | 54 | 0.642 (0.12) | 0.065 (0.02 to 0.11; 0.008) |
| *Complete data*[b] | | | | | |
| Baseline | 53 | 0.685 (0.10) | 54 | 0.720 (0.09) | -0.035 (-0.07 to 0.00; 0.063) |
| 24-month follow-up | 53 | 0.710 (0.12) | 54 | 0.642 (0.12) | 0.068 (0.02 to 0.12; 0.005) |
| QALYs | 53 | 1.355 (0.17) | 54 | 1.323 (0.14) | 0.032 (-0.03 to 0.09; 0.298) |
| QALYs (cont.)[c] | - | - | - | - | 0.069 (0.02 to 0.12; 0.005) |
| **Late recruitment** | | | | | |
| *Observed data* | | | | | |
| Baseline | 59 | 0.659 (0.14) | 50 | 0.633 (0.12) | 0.025 (-0.02 to 0.07; 0.303) |
| 24-month follow-up | 46 | 0.690 (0.14) | 44 | 0.691 (0.14) | -0.001 (-0.06 to 0.06; 0.968) |
| *Complete data*[b] | | | | | |
| Baseline | 46 | 0.654 (0.13) | 44 | 0.625 (0.12) | 0.029 (-0.02 to 0.08; 0.279) |
| 24-month follow-up | 46 | 0.690 (0.14) | 44 | 0.691 (0.14) | -0.001 (-0.06 to 0.06; 0.968) |
| QALYs | 46 | 1.307 (0.18) | 44 | 1.277 (0.18) | 0.029 (-0.05 to 0.11; 0.444) |
| QALYs (cont.)[c] | - | - | - | - | 0.001 (-0.06 to 0.06; 0.963) |

CI indicates confidence interval; cont., controlled; iCDM, internet chronic disease management; n, number; QALY, quality-adjusted life year; sd, standard deviation.

[a] Mean difference calculated as the intervention group estimate minus the control group estimate.
[b] 'Complete data' samples include respondents providing SF-6D scores at baseline and 24 months.
[c] Incremental QALY estimate after controlling for baseline SF-6D score.

The incremental QALY estimate after controlling for baseline SF-6D scores for the ‘early’ group was 0.069, i.e., the point estimate was in favour of the iCDM package (95% CI, 0.02 to 0.12; p = 0.005). The corresponding incremental QALY estimate in the ‘late’ group was 0.001; the point estimate was still in favour of the iCDM program, albeit negligibly different from zero (95% CI, -0.06 to 0.06; p = 0.963). Baseline SF-6D scores explain this variation in incremental QALY estimates. In the ‘early’ group, baseline SF-6D scores were higher in the usual care group. In the 'late’ group, baseline SF-6D scores were higher in the iCDM group. Additionally, regardless of treatment group, the ‘early’ group, baseline SF-6D overall mean score is significantly higher in comparison to the ‘late’ group (mean difference 0.063, 95% CI, 0.03 to 0.09; p = 0.000). Based on these results, it seems likely that the different conclusions drawn from EQ-5D-5L-derived QALY estimates and SF-6D-derived QALY estimates are because of differences in baseline SF-6D scores between those recruited ‘early’ and ‘late’.

### 3.3.5. Analysis of the SF-6D baseline dimension responses before and after the addition of EQ-5D-5L

To explore the extent to which the differences in baseline SF-6D scores between those recruited ‘early’ and ‘late’ were captured by the instrument, SF-6D dimension-level responses at baseline were analyzed. Table 3.8 reports response patterns at baseline for SF-6D dimensions for people recruited before and after the addition of EQ-5D-5L. In general, respondents recruited late reported having more limitations in comparison to the early recruitment group. The greatest differences occurred between the early and late recruitment groups regarding role limitations, social functioning, pain, and mental health. When it comes to the patients recruited early, 37.4% had no problems with role limitation, in contrast to 24.4% of the patients recruited late. Furthermore, 50.5% of the patients recruited early had no limitation with their social functioning, while, respectively, 32.2% of the patients recruited late had no limitation regarding social functioning. Regarding pain, only 1% of patients recruited early had pain that interferes with normal work extremely. In contrast, 10% of patients who were recruited late had pain that interferes with normal work extremely. When it comes to mental health, 25.5% of the patients recruited early did not feel tense or downhearted any of the time, contrary to 12.2% of the patients recruited late. Dimension-level responses equal to or greater than

50%, for the highest or lowest level, were observed for the early recruitment group (level 1: social functioning).

**Table 3.8: Number (percentage) of responses for each level of severity for the SF-6D at baseline, for patients recruited before and after the addition of the EQ-5D-5L as a study outcome.**

| Baseline SF-6D Dimension | Level 1 | Level 2 | Level 3 | Level 4 | Level 5 | Level 6 |
|---|---|---|---|---|---|---|
| Early recruitment | | | | | | |
| PF | 6 (5.6) | 28 (25.2) | 41 (38.3) | 12 (11.2) | 18 (16.8) | 3 (2.8) |
| Role limitations | 40 (37.4) | 40 (37.4) | 4 (3.7) | 23 (21.5) | - | - |
| SF | 54 (50.5) | 23 (21.5) | 26 (24.3) | 3 (2.8) | 1 (0.9) | - |
| Pain | 10 (9.3) | 21 (19.6) | 29 (27.1) | 38 (35.5) | 8 (7.5) | 1 (0.9) |
| Mental health | 27 (25.2) | 42 (39.3) | 31 (29.0) | 7 (6.5) | 0 (0.0) | - |
| Vitality | 2 (1.9) | 32 (29.9) | 39 (36.4) | 24 (22.4) | 10 (9.3) | - |
| Late recruitment | | | | | | |
| PF | 5 (5.6) | 35 (38.9) | 15 (16.7) | 8 (8.9) | 20 (22.2) | 7 (7.8) |
| Role limitations | 22 (24.4) | 22 (24.4) | 12 (13.3) | 34 (37.8) | - | - |
| SF | 29 (32.2) | 14 (15.6) | 29 (32.2) | 15 (16.7) | 3 (3.3) | - |
| Pain | 11 (12.2) | 16 (17.8) | 16 (17.8) | 18 (20.0) | 20 (22.2) | 9 (10.0) |
| Mental health | 11 (12.2) | 37 (41.1) | 33 (36.7) | 7 (7.8) | 2 (2.2) | - |
| Vitality | 1 (1.1) | 21 (23.3) | 30 (33.3) | 17 (18.9) | 21 (23.3) | - |

PF indicates physical functioning; SF, social functioning.

'Highest level'=no impairment (level 1 response), 'lowest level'=greatest degree of impairment (level 6 response for physical functioning and pain, level 5 response for social functioning, mental health, and vitality, level 4 response for role limitations. A dash ('-') indicates that the response level does not exist.

## 3.3.6. Sensitivity analysis

Results of the one-way sensitivity analysis, which consisted of varying the costs of hospital visits, are presented in Table 3.9 for the complete case data set. The equivalent sensitivity analysis results for the observed data set are provided in Appendix B.9. There were no statistically significant differences in the mean hospital visit costs when non-age specific full hospital and physician cost per episode of care in BC hospitals are analyzed.

**Table 3.9: One-way sensitivity analysis for hospital visit cost between iCDM and usual care over 24 months, for the complete case data set. Values are mean (standard deviations) costs unless stated otherwise.**

| Item of resource | iCDM (n=106) | Usual care (n=104) | Mean difference[a] (95% CI; p value) |
|---|---|---|---|
| **Inpatient services** | | | |
| *Hospital visit* | | | |
| Sensitivity analysis | | | |
| B to 12M | 4455.70 (9177.08) | 6234.26 (18345.10) | -1778.56 (-5713.77 to 2156.65; 0.374) |
| 12M to 24M | 4009.82 (10024.56) | 5484.99 (10879.14) | -1475.17 (-4320.33 to 1370.00; 0.308) |
| B to 24M | 8347.88 (14555.96) | 11558.33 (22830.16) | -3210.45 (-8409.26 to 1988.36; 0.225) |
| Base case | | | |
| B to 12M | 4629.16 (9478.40) | 6274.06 (18001.63) | -1644.91 (-5548.55 to 2258.73; 0.407) |
| 12M to 24M | 4106.90 (10329.45) | 5697.17 (11200.58) | -1427.79 (-4520.65 to 1340.11; 0.286) |
| B to 24M | 8615..57 (15117.36) | 11804.09 (23163.20) | -3336.28 (-8862.48 to 1442.75; 0.157) |

B indicates baseline; iCDM indicates internet chronic disease management; M, months; n, number.

[a] Differences in mean values were calculated as values for patients receiving iCDM minus values for patients receiving usual care.

## 3.4. Discussion

This is the second Canadian study looking at the cost-effectiveness of DHIs for patients with multimorbidity, and the first *trial-based* economic evaluation. This CCA assessed the cost and consequences of the iCDM program in comparison to usual care for patients from small urban and rural areas who have multimorbidity. In general, throughout the entire follow-up, the iCDM intervention was less costly than usual care. For all three follow-up periods (baseline to 12 months, 12 months to 24 months, and baseline to 24 months), the higher total cost estimation in the usual care group was largely because of hospital visits. Due to the limited number of resources included in the cost analysis, it is difficult to make a definitive conclusion concerning the cost saving nature of the iCDM program. Overall, iCDM had a positive effect on a number of outcomes, but the effect of iCDM on health-related quality of life was mixed. The EQ-5D-5L results were in favour of the usual care group, although not significantly. On the other hand, the SF-6D findings were significantly in favour of the iCDM group. When it comes to outcomes not related to health, patients in the iCDM group showed significant improvements in comparison to usual care in terms of one domain of MOS Social Support Survey (emotional and informational support), two domains of heiQ (skill and technique acquisition, and emotional wellbeing), and SF-36 (emotional wellbeing).

The significant improvements observed in the skill and technique acquisition domain of the heiQ indicate that the iCDM intervention is beneficial for patients in terms of developing skills in symptom relief and techniques to manage their own health.[128] This is an important finding considering that self-management interventions, such as iCDM, should enhance a patient's ability to manage their conditions.[150] The significant improvements observed in one of the social support domains (emotional and informational support) of the MOS Social Support Survey suggest that the iCDM intervention is helpful for patients with multimorbidity with regard to their mental wellbeing.[151] A recent longitudinal study from Germany examined the relationship between multimorbidity and social support and found that social support helps in maintaining mental wellbeing of patients with multimorbidity.[151] Because of this, the authors recommended increasing social support should be an important goal of interventions targeting multimorbidity, such as iCDM.[151] Regarding the preference-based outcomes, as mentioned earlier in the chapter, there was a difference in the direction of

the incremental QALY estimate when using the EQ-5D-5L and SF-6D. The EQ-5D and SF-6D both measure HRQoL. However, there are differences; the SF-6D is more focused on social aspects of health, while the EQ-5D focuses more on physical aspects of health in the context of chronic conditions.[152–154] The fact that there is a difference in the results when using the two instruments (i.e., EQ-5D-5L in favour of usual care, and SF-6D in favour of iCDM) suggests that social aspects of health were improved by the iCDM intervention.

The concept of 'clinically important' or 'minimally important' differences (MIDs) in the study outcomes also warrants consideration. There are a number of published MID estimates for the EQ-5D-5L and SF-6D,[155–157] although the utility of such estimates within the framework of economic evaluation is negligible[158] and some health economists have questioned whether the idea of an MID for a generic preference-based instrument has any merit, in any context.[159] Of relevance here is the argument against the usefulness of MIDs (or any external benchmark to judge the 'importance' of a change in health outcome) in economic evaluation. Essentially, the key issue is that knowledge of the magnitude of a change in outcome is insufficient, on its own, to inform decision-making. To assess cost-effectiveness, there also needs to be the simultaneous consideration of the costs of treatment options and, importantly, the incremental cost that is associated with the incremental benefits. This is true whether exploring cost-effectiveness in a disaggregated format (i.e., CCA) or when estimating an incremental cost-effectiveness ratio. While authors have written about these issues when referring to preference-based instruments, the same objections apply to any outcomes when analyzed in an economic evaluation framework. A distinct issue regarding MIDs, although related due to the clinical context of the iCDM trial, is the questionable merit of using MIDs for generic outcomes in the area of multimorbidity. The heterogeneity of multimorbidity, with patients experiencing a variety of co-existing conditions and severities of conditions, challenges the concept of a single, universally applicable MID. Finally, on this topic of 'clinical relevance' or 'clinical importance', it is worthwhile to revisit the purpose of examining cost-effectiveness using CCA. CCA is a largely descriptive analysis, with all outcomes (cost and benefits) present in a disaggregated format. The decision whether to adopt an intervention is based on decision-makers' own values and their own understanding of the results.[61] External benchmarks, such as MID estimates, *which are interpreted as*

*being applicable at the individual patient-level*, is very different to a consideration of what is important at a societal level.

The way in which deaths during the study follow-up could have affected the cost estimates in regard to the timing of death is important to consider. If a patient dies earlier in the study, they would not have used healthcare resources for as long as someone who survives the entire study period. For example, nine patients who died during the first year of follow-up in the RCT discussed in Chapter 3, would not have utilized healthcare resources as long as patients who survived two years of follow-up. This could lead to an underestimation of costs for the group with earlier deaths, as they had less opportunity to utilize healthcare resources. Some aspects of the iCDM intervention should also be reflected on when interpreting the results of this economic evaluation. The iCDM program is not targeted to patients with a specific disease, but rather to a population with specific multimorbidity. Therefore, the cost-effectiveness of the iCDM program may be different for patients with different chronic illnesses, considering their complex needs and individual circumstances.[102]

Two economic evaluations that looked at the affects of DHIs in people with multimorbidity found them to be more costly than the standard care, which is different to the results reported in this chapter.[91,92] Despite these findings, Gayot et al.[85] examined the costs of a preventative geriatric telemedicine program and found that the intervention was less costly than usual care, which is consistent with our findings. These findings suggest that there is still currently mixed evidence on the costs of DHIs for people with multimorbidity. An economic evaluation from England also examined EQ-5D-5L as an outcome measure for a DHI for people with multimorbidity.[92] Contrary to our findings, it reported that a telephone health coaching program was associated with more QALYs in comparison to the usual care group. The findings that are consistent with our economic evaluation come from Ontario, where it was found that their DHI was also associated with fewer QALYs in comparison to the usual care group.[91]

### 3.4.1. Strengths and limitations

The main strengths of this economic evaluation comprise the breadth of outcomes assessed, the disaggregation (and transparency) of outcomes in the form of a CCA, and reduced recall bias. In this analysis, five outcomes were evaluated, which would help decision-makers, clinicians, and researchers understand the impact of the interventions on patients. A particular strength related to outcomes is that two of the five outcome measures were preference-based measures (EQ-5D-5L and SF-6D). If the CCA only included the SF-6D measure, and EQ-5D-5L data was not administered one-year post-recruitment, a different conclusion would have been reached regarding the effectiveness of iCDM intervention. Unit cost estimates in this analysis were received from publicly available sources and results were presented in a disaggregated form so that decision-makers can independently draw conclusions, rather than using other methods such as cost-utility or cost-effectiveness analysis where calculations result in a single final cost and outcome number.[160] There is a possibility of recall bias as patients in the RCT were asked over a telephone interview to recall their service use over the past year. This bias was reduced by confirming patients' hospital records after a telephone interview.

As with all studies, this economic evaluation has numerous limitations. First, the SF-6D data was not collected at each follow-up assessment, since the questionnaire was administered at baseline and 24-months post-recruitment only. This means health changes that occurred between baseline and the 24-month follow-up were not captured. Second, when it comes to the SF-6D outcome data, the UK value set was used since a Canadian one was not available. This is problematic since estimates elicited from the UK population might not be representative of the Canadian population. For example, valuations could be different between two populations because of distinctions in economy, culture, or different socio-economic factors.[161] Third, this economic evaluation included several outcome measures (five in total) and multiple comparisons. While the breadth of outcomes assessed provides a comprehensive picture of the effectiveness of the iCDM intervention, it is important to acknowledge that conducting multiple comparisons raises the possibility of type I errors, where statistically significant results may occur by chance.

Fourth, the data collected in the RCT on the use of medications, vitamins, diagnostic tests, and laboratory services was not costed. Unlike resource use data for the clinic,

hospital, and ED visits (which was costed), the difference lies in the timeframe of the questions in the study surveys. For questions about clinic, hospital, and ED visits, participants were asked about their resource use in the previous year. This timeframe accurately captures the use of a resource during a specific time period. However, for medications and vitamins, participants were asked about their *current* use at 24-month follow-up. This timeframe (i.e., "currently") does not capture the use of a resource during a time period, but rather at a single time point. For diagnostic tests and laboratory tests, participants were asked to recall the previous 90 days. Again, this timeframe does not accurately capture the use of these resources during the entire follow-up period of the study (only a snapshot). If some assumptions had been made, these data could have been included. For example, the assumption could have been made that 'current use' is a proxy for 'use during the 24 months' (e.g., the 24-month data could be assumed to be a good approximation for any time point during the period of follow-up). Another possibility was to look for information about the average length of time that patients take certain medications and vitamins, and use that information for a duration estimate. A similar assumption could have been made that 'diagnostic tests and laboratory tests conducted in the last 90 days' is a proxy for 'diagnostic tests and laboratory tests conducted in the previous year'. The level of uncertainty concerning these assumptions was deemed sufficiently high that the cost analysis focused only on resource use data that matched the follow-up period of the study. The absence of these resource use data, however, makes it difficult to determine the true magnitude of publicly-funded healthcare payer costs. For example, excluding medications, diagnostic tests and laboratory tests will lead to an underestimation of the overall costs in both the iCDM and usual care groups. This is due to the fact that patients living with multimorbidity use considerably more prescription medications and have higher prescription drug expenses than individuals living with a single chronic disease.[103] Additionally, patients living with multimorbidity incur higher diagnostic tests and laboratory tests costs compared to non-multimorbid patients.[162,163] Whether the absence of costing these resources would increase or decrease the cost difference between the iCDM and usual care groups warrants consideration. Overall, there was a pattern of greater use of medications, vitamins, diagnostic tests, and laboratory tests at 24-month follow-up in the iCDM group compared with the usual care group (see Appendix B.8), suggesting that the incremental cost difference would reduce, had these resources been costed.

Fifth, primary care visits were not asked about in study surveys, which is a notable limitation. Primary care visits constitute a significant cost component for patients with multimorbidity, since having multimorbidity more than doubles the expected use of primary care in comparison with having zero or one chronic condition.[164] Primary care consultations also significantly increase with an increasing number of chronic conditions, leading to higher healthcare utilization and costs.[165] For these reasons, the omission of primary care visits likely led to an underestimation of the overall costs of both groups in this economic evaluation. It remains uncertain whether primary care visits would influence the cost differential between the iCDM and the usual care group. The literature is mixed on whether multimorbidity-focused interventions, such as iCDM, reduce primary care visits, with some interventions leading to reduced primary care visits,[86,89] whilst some do not.[82,92,96,166]

Sixth, the costs of the iCDM intervention itself, accounting for the resources associated with the design and delivery of the program (e.g., staff time [nurses, exercise specialists, and dietitians] for program delivery, training of staff, and overhead) were also not included in the economic evaluation. The absence of these costs is a significant limitation. By definition, including costs related to the design and delivery of the iCDM intervention would make the program more expensive and, therefore, reduce the observed cost saving estimate when compared with usual care. Further work would be needed to cost the iCDM intervention itself if decision-makers were considering implementing the program.

Finally, the data on the use of social care services were not collected in the RCT. If decision-makers were interested in costs to government payer beyond healthcare, exact estimates may not be obtained because no information was collected on the use of social care services, which are an important element of care for patients with multimorbidity given the long-term spectrum and complexity of illness.[69]

Further work is needed to understand the merits of alternative preference-based instruments in the complex area of multimorbidity. Additional research is required to determine the long-term cost-effectiveness of digital health interventions (DHIs) for patients with multimorbidity. Societal perspective could also be conducted in further research because disregarding important costs and outcomes in an economic evaluation could lead to an inefficient allocation of resources, both in the short and long-term.[167]

Barnett et al.[168] stressed the importance of including health economists as early as possible in the research project, ideally at the study design stage. This will help ensure rigorous economic evaluations can be conducted. Additionally, since this RCT has only included patients fluent in English, future clinical trials can become more inclusive by removing language prerequisites that lack scientific or ethical justification.[169]

## 3.5. Conclusion

The CCA is the type of economic evaluation that gave the most transparent format for reporting the breadth of outcomes collected in the RCT. Broadly, across multiple different analyses, the iCDM intervention cost less than the usual care comparator, although the difference was not statistically significant. The iCDM intervention also has a positive effect on a number of outcomes. Overall, the iCDM intervention resulted in healthcare cost savings for patients with multimorbidity (albeit with the caveat that some key resources, such as primary care consultations and the resources required to deliver the iCDM intervention, were not costed in the analysis), but there is more nuance in terms of effectiveness. Considering the broad set of outcomes examined in the economic evaluation, a number of outcomes did favour the iCDM intervention, but not all of them.

# Chapter 4.

# Discussion: contribution and significance of the thesis

## 4.1. Novel contributions and significance of the systematic review

Chapter 2 described the first systematic review assessing the evidence for cost-effectiveness of interventions targeted to people with multimorbidity, while defining multimorbidity as the co-existence of two or more chronic conditions within an individual, where one is not necessarily more important than the other(s). This review is significant given the fact that previous reviews mostly examined the cost-effectiveness of comorbidity-focused interventions,[64,65] and that there is still no consensus on the definition of multimorbidity globally, which makes comparing and/or synthesizing studies a challenge.[100] For example, two relevant organizations in Canada and England define multimorbidity in very different ways. In the Canadian Community Health Survey, Statistics Canada defined multimorbidity as "*having three or more of the selected chronic conditions: arthritis, high blood pressure, diabetes, cancer (ever diagnosed), heart disease (ever diagnosed), stroke, mood disorders and anxiety".*[1] NICE has defined multimorbidity as the *"presence of two or more long-term health conditions".*[2] The findings from the review provided further evidence of the absence of a consensus on the definition of multimorbidity. The most common definition of multimorbidity described in economic evaluations captured in the review represented it as having two or more chronic conditions. Some did not provide a definition at all, and only one definition aligned with the definition used in the review. The studies whose definitions did not align with the definition used in the review were still included if it was confirmed that the population in these studies indeed consists of individuals with two or more chronic conditions, where one is not necessarily more important than the other(s). Because of the distinction between comorbidity and multimorbidity that has emerged, a multimorbidity-focused review of economic evaluations was warranted. This is primarily

because of the different focus that multimorbidity-focused interventions need to adopt in comparison to comorbidity-focused interventions. More specifically, multimorbidity-focused interventions should have a more generic focus that works across a different range of conditions, while comorbidity-focused interventions focus on specific conditions occurring together and assess outcomes related to those particular diseases.[24]

The systematic review evaluated the reporting standards and quality appraisal of the included economic evaluations by using two checklists, CHEERS 2022 and QHES. This is significant, given that only 26% of systematic reviews of health economic evaluations use two or more checklists, according to a 2019 *Value in Health* paper.[112] Another significance is that this review did not apply arbitrary cutoffs to indicate quality when it comes to CHEERS 2022. Scoring cutoffs were applied in the case of QHES, which is recommended by its developers.[78] It is recommended by Watts and Li, the authors of the 2019 *Value in Health* paper, that authors of reviews do not provide arbitrary cutoffs since most checklists do not mention or advise against providing a score to indicate the quality of the review. However, among the included reviews in a 2019 *Value in Health* paper, 49.1% of them present a score even when the QHES checklist is excluded.[112] This is also problematic since a 2019 *Value in Health* paper found cutoffs that represented "high quality" spanned from 63% to 94%, and most likely an economic evaluation that has a score of 63% does not have the same quality as the study with 94%, no matter how quality is defined. Another recommendation from a 2019 *Value in Health* paper is that within one's subject area, such as reviews of economic evaluations in the area of diabetes, reviewers should use the same checklist(s) utilized in previous reviews. The systematic review reported in Chapter 2 followed this recommendation and used both checklists utilized in two previous systematic reviews of economic evaluations in the subject area of multimorbidity.

Another novel aspect of the systematic review is the inclusion of CCAs. In contrast with other reviews, this review identified five CCAs, while others have included none (because CCA was not part of their inclusion criteria).[64,65] The reason(s) behind excluding CCAs in the other two reviews was not mentioned. The benefits of including the CCAs in systematic reviews focusing on cost-effectiveness of multimorbidity-focused interventions have been described in detail in the Discussion section of Chapter 2. Mauskopf and colleagues believe that CCAs can be of most value to decision-makers in comparison to other types of economic evaluation.[62] The question has been raised by

Mauskopf and colleagues regarding the usefulness of economic evaluations in healthcare, considering that information presented is often not in a format that is understandable and/or usable by non-economists. They argue that CCA is the most useful type of economic evaluation for decision-makers since it gives the most comprehensive presentation of information describing the value of an intervention and is conceptually the simplest. Because of this, and the benefits of including CCAs in systematic reviews focusing on the cost-effectiveness of multimorbidity-focused interventions mentioned in Chapter 2, the inclusion of CCAs in this systematic review is considered a significant strength.

## 4.2. Novel contributions and significance of the cost-consequence analysis

The evidence from Chapter 2 suggested that CCA may be a well-suited form of economic evaluation in the context of multimorbidity. It also indicated that interventions containing a self-management support component, either as a main or secondary focal point, are likely to be cost saving options for people with multimorbidity. In Chapter 3, the second Canadian study looking at the cost-effectiveness of a DHI with a self-management support component, for patients with multimorbidity (and the first *trial-based* economic evaluation) was reported.

An important aspect of this thesis is that an RCT has a focus on Canadians from small urban and rural areas. In Canada, health-related strategic plans and policies often prioritize urban areas, while neglecting the distinct needs and challenges of rural communities.[170] Stakeholders with corporate and commercial interests frequently perceive rural markets as unprofitable and unappealing, exacerbating the vulnerabilities and disadvantages faced by these populations. In contrast to individuals living in urban environments, rural residents often encounter obstacles such as limited access to higher education, employment opportunities, public funding, and comprehensive healthcare services. In regard to healthcare, the data from the Canadian Longitudinal Study on Aging, a population-based, 20-year prospective cohort study indicates that Canadians living in rural areas are less likely to see a family doctor and a specialist physician, and more likely to visit an ED, than urban Canadians.[171] Canadians from rural areas also experience higher rates of mortality and hospitalization.[119–121] As discussed in the introduction of Chapter 3, compared to Canadians who live in urban areas, those who

reside in rural areas have a higher prevalence of risk factors that contribute to or exacerbate chronic conditions such as smoking, obesity, and poor nutrition. The overwhelming healthcare and non-healthcare related challenges that rural Canadians are facing, strengthen the case for trial-based economic evaluation in Chapter 3, given the trial's inclusion of Canadians from rural areas.

Another significance of this work is that in this economic evaluation, both health (QALYs) and non-health (self-management, social support, and quality of life) outcomes have been assessed. In the other Canadian economic evaluation looking at the cost-effectiveness of a DHI with a self-management support component, only QALYs were used as the measure of health outcome.[91] To date, there has been no review about how the effects of DHIs should be measured in cost-effectiveness analyses, including the rationale of using QALYs and other generic outcome measures in this domain.[172] In the case of DHIs, regulatory agencies such as NICE recommend the use of CCA when these types of interventions trigger both health and non-health benefits, which are challenging to combine into a single measure, such as QALY.[63,172] Decision-makers can also find CCA beneficial in the context of DHIs, since some may place higher value on the effects of DHIs reducing health inequalities, while others may emphasize the role of DHIs in enhancing the efficiency of healthcare delivery.[63]

The economic evaluation adds to the limited evidence base on the cost-effectiveness of self-management support interventions for patients with multimorbidity. For example, as reported in the systematic review in Chapter 2, four economic evaluations[81,86,91,92] reported the cost-effectiveness of self-management support interventions, and the majority (n=3) found these interventions to be cost-effective.[81,86,92] The results from the economic evaluation conducted in Chapter 3 further highlight the potential for self-management interventions to be cost saving for patient populations with multimorbidity. However, there was more nuance in terms of evidence for the effectiveness of iCDM. Considering the broad set of outcomes examined in the economic evaluation, a number of outcomes did favour the iCDM intervention, but not all of them.

Comparing the findings of the economic evaluation conducted in Chapter 3 with the systematic review from Chapter 2 findings suggests a role of the medication adherence component in the cost-effectiveness of multimorbidity interventions. Medication adherence occurs when patients take their medications as prescribed, and it is crucial in

achieving optimal disease control.[173] A high level of medication adherence among patients with chronic diseases is associated with lower disease-related medical costs.[174] The results from the systematic review indicate that incorporating medicines management into multimorbidity interventions may be an important driver of cost-effectiveness, due to cost savings and improved health outcomes associated with this component. In fact, in the CCA, one of the components of the iCDM intervention was medication adherence. As explained in the Methodology section, as part of the alert system, the patients in the trial were prompted to answer questions regarding their medication adherence. The question pertaining to medication adherence was, "*Are you able to take your medications at the correct dose and time more than 80% of the time?*". If the answer was no, the alert was activated, and the patient received additional support/counselling from the nurse assigned to them, such as general counselling which may include titration of medications. As discussed in the literature, titration of medications could lead to better medication adherence.[175,176] Given that the question about medication adherence was part of the alert system component of the intervention and not part of the questions asked in study surveys, there is no data available regarding the patient responses to this question in the iCDM group. Nevertheless, general counselling, which included titration of medications, could have been a factor in the iCDM cost saving nature in comparison to usual care.

Chapter 3 further expands the knowledge on the CCA in the area of multimorbidity. As discussed in Chapter 2, findings from the systematic review suggest that CCA may be a form of economic evaluation well-suited to the context of multimorbidity – primarily because of the challenges in measuring outcomes in multimorbidity interventions. In 2023, a CCA of a multimorbidity patient-centred care model (MPCM) compared to usual care was conducted in Chile.[166] Along with the same type of analysis, this economic evaluation shares other similarities to the economic evaluation conducted in Chapter 3. The perspective was that of the publicly funded healthcare payer, and one of the focus areas of the intervention was the self-management of chronic conditions. Findings from the Chilean economic evaluation suggested that MPCM was a cost saving intervention and health outcomes were associated with higher survival in patients in the MPCM group. Despite the similarities between the two economic evaluations, an important difference was that the economic evaluation in Chile involved the analysis of more cost

items (primary care visits, implementation, and medications costs) than the economic evaluation from Chapter 3.

## 4.3. Areas for further research

In Chapter 3, the population in the trial-based economic evaluation consisted of patients with multimorbidity only from small urban and rural areas of BC. Therefore, it is not known whether the indicated cost-effectiveness of the iCDM intervention in Chapter 3 is different in patients with multimorbidity from urban areas. Both primary care and general population studies suggest that multimorbidity is more prevalent among patients from urban areas than those in rural areas.[177–179] The reasons for this could be attributed to an increase in risk factors like a sedentary urban lifestyle, lack of physical activity, and higher consumption of energy-dense and fatty foods.[177] Furthermore, residing in urban areas offers convenient access to healthcare facilities, which encourages greater health-seeking behaviour.[180] This leads to a quick diagnosis of non-communicable diseases, thereby increasing the prevalence of multimorbidity in urban regions compared to rural areas.[181] To strengthen the evidence base for the cost-effectiveness of DHI with the self-management support component, future trials in BC and Canada could include patients from both large urban and rural areas.

A second important consideration regarding the population in the trial-based economic evaluation was age, with the average age of participants being 70.5 years. Although the burden of multimorbidity is particularly pronounced among older adults, with 2021 estimates suggesting that over 50% of the global adult population aged 60 years and above are affected by multimorbidity,[9] it also affects younger people.[182] Current evidence suggests that the prevalence of youth multimorbidity is high,[183] with population-based studies providing estimates between 20% and 30%.[184] A study from Denmark examined young people (age 14-26) with multimorbidity, and found that compared to those with a single chronic disease, young people with multimorbidity reported lower levels of wellbeing and life satisfaction. Furthermore, they had increased odds for suicidal thoughts, self-harm, and loneliness, along with significantly higher odds for health risk behaviours and psychosocial challenges compared to those with a single chronic

illness.[185] Along with including patients from large urban areas, future RCTs may want to consider including younger multimorbidity patients.

## 4.4. Thesis summary and conclusions

This thesis focused on economic evaluation in the context of multimorbidity. Due to the debate concerning the definition of multimorbidity, and the observation that the current literature primarily focuses on the cost-effectiveness of *comorbidity*-focused interventions, a systematic review was conducted. The objective of the review was to identify and describe the economic evaluation literature regarding multimorbidity-focused interventions, defining multimorbidity as the co-existence of two or more chronic conditions within an individual, where one is not necessarily more important than the other(s). Findings from the systematic review pointed out a great degree of heterogeneity across published economic evaluations in the area of multimorbidity in terms of the definition of multimorbidity, intervention types, included chronic conditions, types of economic evaluation, examined outcomes, and quality across the studies. The identified evidence suggested that CCA is likely to be well suited to the challenges of conducting economic evaluation in the context of multimorbidity. In Chapter 3, a trial-based CCA was undertaken to determine the costs and outcomes associated with usual care and a digital health-based self-management program in a sample of adults with multimorbidity living in small urban and rural areas of BC. While the findings revealed healthcare cost savings associated with the iCDM intervention for patients with multimorbidity (with the caveat about resources that were not costed, such as the resources required to deliver the iCDM intervention), the picture regarding effectiveness is more nuanced. Across the range of outcomes assessed in the economic evaluation, some did demonstrate positive effects for the iCDM intervention, but not all. Overall, this thesis highlights the need for standardized definitions and methodologies in economic evaluations of multimorbidity interventions to allow comparisons between studies and guide future resource allocation decisions in a more straightforward way.

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# Appendix A. Appendices to Chapter 2

**Appendix A.1: Search strategy (with number of identified publications for each search term), as applied to the MEDLINE database on the Ovid platform.**

| | Search terms | Number of publications identified |
|---|---|---|
| 1 | health econom*.ti,ab. | 10,290 |
| 2 | economic* evaluation*.ti,ab. | 14,427 |
| 3 | economic* analys#s.ti,ab. | 7,905 |
| 4 | cost effect*.ti,ab. | 165,505 |
| 5 | cost-effect*.ti,ab. | 165,505 |
| 6 | cost benefit*.ti,ab. | 12,437 |
| 7 | cost-benefit*.ti,ab. | 12,437 |
| 8 | cost utilit*.ti,ab. | 5,668 |
| 9 | cost-utilit*.ti,ab. | 5,668 |
| 10 | cost consequence* analys#s.ti,ab. | 324 |
| 11 | cost-consequence* analys#s.ti,ab. | 324 |
| 12 | cost minimi#ation analys#s.ti,ab. | 853 |
| 13 | cost-minimi#ation analys#s.ti,ab. | 853 |
| 14 | economic* aspect*.ti,ab. | 3,372 |
| 15 | health care cost*.ti,ab. | 16,438 |
| 16 | cost analys#s.ti,ab. | 8,486 |
| 17 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 | 216,522 |
| 18 | comorb*.ti,ab. | 212,307 |
| 19 | co-morb*.ti,ab. | 31,821 |
| 20 | multiple chronic conditions.ti,ab. | 1,454 |
| 21 | multimorbidity.ti,ab. | 6,281 |
| 22 | multimorb*.ti,ab. | 7,523 |
| 23 | multi-morb*.ti,ab. | 1,103 |
| 24 | multi-morbidity.ti,ab. | 765 |
| 25 | chronic conditions multiple.ti,ab. | 15 |
| 26 | multiple chronic health conditions.ti,ab. | 80 |
| 27 | multiple chronic medical conditions.ti,ab. | 59 |
| 28 | multiple chronic illnesses.ti,ab. | 122 |
| 29 | chronic illnesses multiple.ti,ab. | 7 |
| 30 | multiple chronic diseases.ti,ab. | 596 |
| 31 | multidisease.ti,ab. | 73 |
| 32 | multidiseases.ti,ab. | 0 |

| | Search terms | Number of publications identified |
|---|---|---|
| 33 | multiple condition.ti,ab. | 49 |
| 34 | complex needs.ti,ab. | 1,998 |
| 35 | concurrent chronic conditions.ti,ab. | 25 |
| 36 | concurrent chronic diseases.ti,ab. | 31 |
| 37 | concurrent chronic disorders.ti,ab. | 3 |
| 38 | concurrent chronic health conditions.ti,ab. | 2 |
| 39 | concurrent chronic illnesses.ti,ab. | 6 |
| 40 | concurrent chronic medical conditions.ti,ab. | 2 |
| 41 | multiple chronic disorders.ti,ab. | 18 |
| 42 | simultaneous chronic illnesses.ti,ab. | 0 |
| 43 | simultaneous chronic medical conditions.ti,ab. | 1 |
| 44 | 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 | 251,837 |
| 45 | 17 and 44 | 4,509 |
| 46 | limit 45 to dt=19900101-20230228 | 4,501 |

Ab indicates abstract; dt, date created; ti, title.

**Appendix A.2: 'Guidance for reporting' each item, as described by the CHEERS 2022 ISPOR Good Research Practices Task Force (Husereau et al, 2022).**

| |
|---|
| 1. Identify the study as an economic evaluation and specify the interventions being compared. |
| 2. Provide a structured summary that highlights context, key methods, results, and alternative analyses. |
| 3. Give the context for the study, the study question, and its practical relevance for decision making in policy or practice. |
| 4. Indicate whether a health economic analysis plan was developed and where available. |
| 5. Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics). |
| 6. Provide relevant contextual information that may influence findings. |
| 7. Describe the interventions or strategies being compared and why chosen. |
| 8. State the perspective(s) adopted by the study and why chosen. |
| 9. State the time horizon for the study and why appropriate. |
| 10. Report the discount rate(s) and reason chosen. |
| 11. Describe what outcomes were used as the measure(s) of benefit(s) and harm(s). |
| 12. Describe how outcomes used to capture benefit(s) and harm(s) were measured. |
| 13. Describe the population and methods used to measure and value outcomes. |
| 14. Describe how costs were valued. |
| 15. Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion. |
| 16. If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed. |
| 17. Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used. |
| 18. Describe any methods used for estimating how the results of the study vary for subgroups. |
| 19. Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations. |
| 20. Describe methods to characterise any sources of uncertainty in the analysis. |
| 21. Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study. |
| 22. Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions. |
| 23. Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure. |
| 24. Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable. |
| 25. Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study |
| 26. Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice. |
| 27. Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis |
| 28. Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements. |

CHEERS 2022 indicates Consolidated Health Economic Evaluation Reporting Standards 2022.

**Reference:** Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMC Med* 2022; 20: 23.

**Appendix A.3: Quality of Health Economic Studies (QHES) questions and scoring (Roberts et al, 2019).**

| QHES questions | QHES scoring | Maximum weight |
|---|---|---|
| Q1. Was the study objective presented in a clear, specific and measurable manner? | Clear, specific, measurable = 7<br>Any two = 5<br>Anyone = 2<br>None = 0 | 7 |
| Q2. Was the perspective of the analysis (societal, third party, payer, etc.) and reasons for its selection stated? | Perspective stated = 2<br>Reasons stated = 2<br>Both = 4<br>None = 0 | 4 |
| Q3. Were variable estimates used in the analysis from the best available source (i.e., randomized control trial—best, expert opinion worst)? | Randomized control trial = 8<br>Non-randomized control trial = 7<br>Cohort studies = 6<br>Case-control/case report/case series = 4<br>Expert opinion = 2<br>None = 0 | 8 |
| Q4[a]. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? | Yes = 1<br>No = 0 | 1 |
| Q5. Was uncertainty handled by (1) statistical analysis to address random events, and (2) sensitivity analysis to cover a range of assumptions? | Statistical analysis = 4.5<br>Sensitivity analysis = 4.5<br>Both = 9<br>None = 0 | 9 |
| Q6. Was incremental analysis performed between alternatives for resources and costs? | Yes = 6<br>No = 0 | 6 |
| Q7. Was the methodology for data extraction (including the value of health states and other benefits) stated? | Yes = 5<br>No = 0 | 5 |
| Q8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3–5%) and the justification is given for the discount rate? | Time horizon = 3<br>Cost discounting = 1<br>Benefit discounting = 1<br>Justification = 2<br>All but justification = 5<br>All = 7<br>None = 0 | 7 |
| Q9. Was the measurement of costs appropriate and was the methodology for the estimation of quantities and unit costs clearly described? | Appropriateness of cost measurement = 4<br>Clear description of the methodology for the estimation of quantities = 2<br>Clear description of the methodology for the estimation of unit costs = 2<br>All = 8<br>None = 0 | 8 |

| QHES questions | QHES scoring | Maximum weight |
|---|---|---|
| Q10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes? Was justification given for the measures/scales used? | Primary outcome clearly stated = 2<br>Include major short-term outcome = 2<br>Justification = 2<br>All = 6<br>None = 0 | 6 |
| Q11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was the justification given for the measures/scales used? | Yes = 7<br>No = 0 | 7 |
| Q12. Were the economic model (including structure), study methods and analysis and the components of the numerator and denominator displayed in a clear, transparent manner? | Economic model = 2<br>Study methods = 1.5<br>Analysis = 1.5<br>Components of numerator = 1.5<br>Components of denominator = 1.5 All = 8<br>If not a modelling study, done for study methods = 2<br>Analysis = 2<br>Components of numerator = 2<br>Components of denominator = 2<br>All = 8<br>None = 0 | 8 |
| Q13. Were the choice of the economic model, main assumptions and limitations of the study stated and justified? | Economic model = 2<br>Assumptions = 2.5<br>Limitations = 2.5<br>All = 7<br>If not a modelling study, done (stated and justified) for assumptions = 3.5<br>Limitations = 3.5<br>Both = 7<br>None = 0 | 7 |
| Q14. Did the author(s) explicitly discuss the direction and magnitude of potential biases? | Direction = 3<br>Magnitude = 3<br>Both = 6<br>None = 0 | 6 |
| Q15. Were the conclusions/ recommendations of the study justified and based on the study results? | Yes = 8<br>No = 0 | 8 |
| Q16. Was there a statement disclosing the source of funding for the study? | Yes = 3<br>No = 0 | 3 |

QHES indicates quality of health economic studies.

[a] A point was lost if a subgroup analysis was completed and subgroups were not pre-specified in either the protocol or methods section (i.e., if there was no subgroup analysis, a point was assigned as default).

**Reference:** Roberts SLE, Healey A, Sevdalis N. Use of health economic evaluation in the implementation and improvement science fields—a systematic literature review. *Implementation Sci* 2019; 14: 72.

**Appendix A.4: Intervention components.**

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| Basu (2015)[81] | Chronic Disease Self-Management Program (CDSMP) | Facilitators: Delivered CDSMP workshops through 22 licensed sites nationwide (17 states). Workshops were supported by federal, state, and local sources, healthcare organizations, and community agencies.<br>Focus areas:<br>1. techniques to manage typical responses to chronic health problems such as frustration, fatigue, pain, and isolation;<br>2. improving healthy behaviour such as physical exercise for maintaining and improving strength, flexibility, and endurance;<br>3. appropriate use of medications, and effective communication with healthcare professionals. | Self-management support |
| Ekdahl (2015)[82] | Comprehensive geriatric assessment (CGA) | Facilitators: A nurse, a geriatrician/ resident physician, a municipal care manager, an occupational therapist, a physiotherapist, a dietitian, an administrative assistant, a dental hygienist, psychologist.<br>Focus areas:<br>1. training programs conducted by a physiotherapist;<br>2. fall prevention measures performed by a physiotherapist and occupational therapist during home visits;<br>3. optimization of pharmacotherapy with the help of clinical pharmacists. | Care coordination |
| Ekdahl (2016)[83] | Comprehensive geriatric assessment (CGA) | Facilitators: A nurse, a geriatrician/ resident physician, a municipal care manager, an occupational therapist, a physiotherapist, a dietitian, an administrative assistant, a dental hygienist, psychologist.<br>Focus areas:<br>1. training programs conducted by a physiotherapist;<br>2. fall prevention measures performed by a physiotherapist and occupational therapist during home visits;<br>3. optimization of pharmacotherapy with the help of clinical pharmacists. | Care coordination |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| Evans (2021)[84] | Community-based short-term integrated palliative and supportive care intervention (SIPScare) | Facilitators: Practitioners and community healthcare services, including district and community nurses.<br>Focus areas:<br>1. multidimensional person-centred care assessment, then multidisciplinary review and management, with coordination of care usually by a nurse specialist;<br>2. integrated care between the general practitioner and community nursing services though primary care multidisciplinary team review, information sharing on assessments and care and treatment plans. | Care coordination |
| Gayot (2022)[85] | Geriatric telemedicine assessment program (GTLM) | Facilitators: The intervention involved an initial teleconsultation within ten days of inclusion. During this first teleconsultation a care plan was agreed upon by the resident, geriatrician, and nursing home staff and sent to the attending physician.<br>Focus areas:<br>1. three follow-up preventative teleconsultations were performed at 3, 6, and 9 months later which involved screening the geriatric syndromes and readjusting the care plan as necessary;<br>2. if necessary, the following connected devices were used: the stethoscope for cardiac auscultation, a camera for the oral examination and sometimes the 'EKG' for an electrocardiogram for the follow-up of coronary disease or cardiac rhythm or conduction disorders. These examinations aim to limit avoidable non-programmed hospitalizations by avoiding decompensation of comorbidities. | Care coordination |
| Gillespie (2022)[86] | Occupational therapy-led self-management support program | Facilitators: Primary care occupational therapists with input from physiotherapists and pharmacists.<br>Focus areas:<br>1. introduction to self-management, activity, and health and goal-setting;<br>2. fatigue management and healthy eating;<br>3. maintaining physical activity;<br>4. maintaining mental wellbeing;<br>5. managing medications;<br>6. communication and program review. | Self-management support |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| Kari (2022)[87] | People-centred care model (PCCM) | Facilitators: Nurse, pharmacist, general practitioner.<br>Focus areas:<br>1. the purpose of the PCCM was to recognize and treat each patient as a person, encourage her/his active role in collaborative health goal setting and empower multimorbid patients to live well with long-term conditions;<br>2. the PCCM comprised: an at-home patient interview by a named nurse and a pharmacist; completing health (the named nurse) and clinical medication (a pharmacist) reviews; and agreeing on the care and medication plan based on the patient's care targets and needs at an interprofessional team meeting (the named nurse, a pharmacist, and a general practitioner). During the two years of follow-up, care coordination and health support were provided by the named nurse;<br>3. during the same at-home interviews, the named nurse, also utilizing the primary care clinical records, discussed health-related issues and goals with the patients to build therapeutic partnership with the patient and empower her/him to take charge of her/his own health. | Care coordination plus self-management support |
| Lanzeta (2016)[88] | Integrated healthcare model | Facilitators: General practitioner, nurse, reference internist, and liaison nurse.<br>Focus areas:<br>1. the intervention consisted of the implementation of an integrated healthcare model for multimorbid patients based on improving communication between primary care and hospital professionals;<br>2. specifically, intervention group patients were managed by the primary care team (general practitioner and nurse) with the support of a reference internist and a liaison nurse;<br>3. reference internist gave direct support in the Health Centre and ensured smooth and flexible communication with primary care doctors. Moreover, every time patients with multimorbidity went to the hospital they were seen by their assigned internist, regardless of the required service; | Care coordination plus self-management support |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| | | 4. as soon as the patient was identified as being multimorbid the liaison nurse carried out a complete assessment (clinical, functional, psychosocial and quality of life);<br>5. the liaison nurse provided health education to improve self-management of each specific disease. | |
| Lundqvist (2018)[89] | Comprehensive geriatric assessment (CGA) | Facilitators: A nurse, a geriatrician/ resident physician, a municipal care manager, an occupational therapist, a physiotherapist, a dietitian, an administrative assistant, a dental hygienist, psychologist.<br>Focus areas:<br>1. training programs conducted by a physiotherapist;<br>2. fall prevention measures performed by a physiotherapist and occupational therapist during home visits;<br>3. optimization of pharmacotherapy with the help of clinical pharmacists. | Care coordination |
| Mercer (2016)[90] | Primary care-based whole-system intervention (CARE Plus) | Facilitators: General practitioner, nurse.<br>Focus areas:<br>1. changes to practice systems to allow longer consultations (30–45 minutes) and relational continuity with eligible multimorbid patients. Each practice decided what changes would be necessary to allow this; provided that they achieved the intended aims, practices were allowed to decide on how to implement this in their particular organizational context;<br>2. group-based practitioner support and training to use the longer CARE Plus structured consultations to carry out a holistic assessment, including identification of patient concerns and priorities, a focus on self-management, and agreeing on a care plan;<br>3. additional patient self-management support materials (mindfulness-based stress management CDs, a cognitive behavioural therapy-derived self-help booklet) and written material (also supplied on a CD) about the intervention and the self-help material (available on request from the corresponding author). | Care coordination plus self-management support |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| Miranda (2022)[91] | Electronic patient-reported outcome (ePRO) mobile app | Focus areas:<br>The ePRO tool has two key features:<br>1. My Goals, which allows patients, caregivers, and providers to create goal-oriented patient care plans using a mobile device during a 15-30-minute care planning appointment. Specified-measurable-attainable-realistic time–specific goal principles were used to guide goal setup and include free-form text to write down general feelings on progress; and<br>2. outcome measures, which help patients, caregivers, and providers to monitor patient measures and outcomes (daily, weekly, or monthly) through validated and reliable health status scales such as Patient-Reported Outcomes Measurement Information System (PROMIS), Global Health Scale (GHS), Health Assessment Questionnaire (HAQ), 9-item Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder 7-Item (GAD-7) scale. | Self-management support |
| Panagioti (2018)[92] | Telephone health coaching | Focus areas:<br>The content of the health coaching was based on three core mechanisms:<br>1. telephone health coaching involved support and encouragement to the patient to promote healthy behaviours around diet, exercise, smoking and alcohol, through the provision of information and motivation for long-term conditions. The core health coaching materials include telephone and associated patient tracking and management software, and health coaching scripts for lifestyle support;<br>2. social prescribing involved links to resources in the wider community through the community and voluntary sector. Access to local resources was provided with a self-assessment tool for users to assess their health and social needs, with links to relevant community resources and local support<br>3. low-intensity support for low mood included assessment of common mental health problems, simple lifestyle advice and behavioural techniques to manage mood, and use of appropriate risk assessment protocols. | Self-management support |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| Salari (2022)[95] | Systematic Tool to Reduce Inappropriate Prescribing (STRIP) | Facilitators: Medical doctor and a pharmacist.<br>Focus areas:<br>1. The overall objective of the intervention: a software-assisted approach to pharmacotherapy optimization, namely the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) based on STOPP/START criteria and including STRIP assistant (STRIPA), implemented by an interprofessional team composed of a medical doctor and a pharmacist was to reduce inappropriate prescribing among people with multimorbidity. | Medicines management |
| Thorn (CUA) (2020)[96] | 3D (dimensions of health, depression and drugs) intervention | Facilitators: General practitioner, nurse, pharmacist.<br>Focus areas:<br>1. nurse consultation to identify health problems most important to the patient, issues with quality of life, screening for depression, collecting health data, for example, blood pressure and information relevant to the patient's specific conditions. Health promotion advice provided;<br>2. pharmacist review of medication from medical records, aiming to simplify and optimize drug treatment. Pharmacists were asked to identify non-essential drugs that could be stopped and essential drugs that should be started, and to seek ways to simplify drug treatment regimes, for example, by making all doses once daily;<br>3. general practitioner reviewed data from the nurse and pharmacist, and agreed on a health plan with the patient, which was given to them as a printed copy. | Care coordination plus self-management support |
| Thorn (CCA) (2020)[96] | 3D (dimensions of health, depression and drugs) intervention | Facilitators: General practitioner, nurse, pharmacist.<br>Focus areas:<br>1. nurse consultation to identify health problems most important to the patient, issues with quality of life, screening for depression, collecting health data, for example, blood pressure and information relevant to the patient's specific conditions. Health promotion advice provided;<br>2. pharmacist review of medication from medical records, aiming to simplify and optimize drug treatment. Pharmacists were asked to identify non-essential drugs that could be stopped and essential drugs that should be started, and to seek ways to simplify drug treatment regimes, for example, by making all doses once daily; | Care coordination plus self-management support |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| | | 3. general practitioner reviewed data from the nurse and pharmacist, and agreed on a health plan with the patient, which was given to them as a printed copy. | |
| Vila (2015)[93] | Home care program | Facilitators: One coordinating physician, two geriatricians, two internists, 22 primary care physicians, one coordinating nurse, and 13 nurses.<br>Focus areas:<br>1. within 24 hours after admission to the program, an intervention team consisting of a nurse and an internist or geriatrician visited the individual, performing a complete geriatric evaluation and designing a care plan, which included assessing the need for physiotherapy, caregiver education, social and psychological support, medical and nursing care, changes to drug therapy, and treatment for geriatric syndromes, as well as taking into consideration the individual's and family's wishes and expectations;<br>2. the follow-up team assigned to their care, who customized the frequency of visits to each individual based on the care plan and the individual's status, proactively followed clinically stable individuals. A direct telephone attended by the coordinating nurse was available to patients and caregivers 12 hours a day (8:00 a.m. to 8:00 p.m.). During the time period that the program did not cover (8:00 p.m. to 8:00 a.m.), the emergency house call (EHC) team was available for people in the program and for those not in the program;<br>3. if an individual's condition worsened or the family doctor or nurse requested it, the program's coordinator determined immediately which professional should visit the person at home. Within one to six hours, depending on the individual's clinical condition, the intervention team reevaluated the individuals and delivered more-complex treatment (e.g., intravenous drug therapy, oxygen therapy), following standardized criteria and protocols. | Care coordination |
| Zimmerman (2017)[94] | Home-based care transitions intervention (HBCTI) | Focus areas: | Care coordination plus self-management support |

| Lead author (year) | Intervention | Important elements/ key features | Types of interventions |
|---|---|---|---|
| | | 1. the intervention was initiated prior to hospital discharge. Strategies to promote patient activation, the underlying mechanism, were incorporated into the intervention to engage patients in self-management behaviours. Knowledge, skills, and competencies were enhanced through self-efficacy improvement strategies. The content was tailored to the patient, depending on their specific chronic conditions. Patients were encouraged to start with behaviours that were feasible to achieve, thus offering an opportunity for patients to be successful;<br>2. in addition to dosage (frequency and length of encounters) and nurse interventionist, strategies to increase patient activation varied by group. Those groups with low activation (Groups 1 and 3) were encouraged to take ownership of their care and set small, attainable goals. For those who were more activated (Groups 2 and 4), strategies included anticipatory guidance such as "what if" scenarios, such as preparing for an upcoming event when the normal routine is upset. To address low cognition (Groups 1 and 2), teach-back, pictures, and images were used;<br>3. for all intervention groups, strategies utilized to promote these self-management skills focused around four core components (medication management, personal health record development, red flag identification, and action planning). Coaching and teach-back were incorporated into the strategies. To address chronic disease symptom management, red flags were identified for the self-identified highest priority chronic diseases. Medication management included medication reconciliation at discharge and at each visit to ensure medications were being taken accurately;<br>4. the project director worked closely with the interventionists to ensure the fidelity of the intervention. Weekly meetings were held to enhance communication. Templates were made for intervention materials such as the pill card and action plans to ensure consistency. The project director was available by phone for any questions related to implementing the intervention arms. | |

**Appendix A.5: Quality assessment of the included economic evaluations based on CHEERS 2022 (part 1)**

| Item no. | Basu (2015) [81] | Ekdahl (2015) [82] | Ekdahl (2016) [83] | Evans (2021) [84] | Gayot (2022) [85] | Gillespie (2022) [86] | Kari (2022) [87] | Lanzeta (2016) [88] | Lundqvist (2018) [89] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2 | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 4 | No | No | No | No | No | No | No | No | No |
| 5 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 7 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 8 | No | No | No | No | Yes | Yes | Yes | No | Yes |
| 9 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10 | NA | No | No | NA | NA | NA | No | NA | Yes |
| 11 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 13 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 14 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 15 | No | Yes | Yes | Yes | No | Yes | Yes | No | Yes |
| 16 | NA | NA | NA | NA | NA | NA | NA | NA | Yes |
| 17 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 18 | Yes | No | No | No | No | Yes | No | No | Yes |
| 19 | No | No | No | No | No | No | No | No | No |
| 20 | No | Yes | No | Yes | No | Yes | Yes | Yes | Yes |
| 21 | No | No | No | No | No | No | No | No | No |
| 22 | NA | NA | NA | NA | NA | NA | NA | NA | Yes |
| 23 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| 24 | No | Yes | No | Yes | No | Yes | Yes | Yes | Yes |
| 25 | No | No | No | No | No | No | No | No | No |
| 26 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 27 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

| Item no. | Basu (2015) [81] | Ekdahl (2015) [82] | Ekdahl (2016) [83] | Evans (2021) [84] | Gayot (2022) [85] | Gillespie (2022) [86] | Kari (2022) [87] | Lanzeta (2016) [88] | Lundqvist (2018) [89] |
|---|---|---|---|---|---|---|---|---|---|
| 28 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

CCA indicates cost-consequence analysis; CHEERS 2022, Consolidated Health Economic Evaluation Reporting Standards 2022; CUA, cost-utility analysis; NA, not applicable; No, number.

**Appendix A.6: Quality assessment of the included economic evaluations based on CHEERS 2022 (part 2)**

| Item no. | Mercer (2016) [90] | Miranda (2022) [91] | Panagioti (2018) [92] | Salari (2022) [95] | Thorn (CUA) (2020) [96] | Thorn (CCA) (2020) [96] | Vila (2015) [93] | Zimmerman (2017) [94] |
|---|---|---|---|---|---|---|---|---|
| 1 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 4 | No | No | No | Yes | No | No | No | No |
| 5 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 7 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 8 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| 9 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10 | NA | No | Yes | NA | Yes | Yes | No | NA |
| 11 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 13 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 14 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 15 | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| 16 | NA | Yes | NA | Yes | NA | NA | NA | NA |
| 17 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 18 | No | No | No | Yes | No | No | No | No |
| 19 | No | No | No | No | No | No | No | No |
| 20 | Yes | Yes | Yes | Yes | Yes | No | No | No |
| 21 | No | No | No | No | No | No | No | No |
| 22 | NA | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 23 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| 24 | Yes | Yes | Yes | Yes | Yes | No | No | No |
| 25 | No | No | No | No | No | No | No | No |
| 26 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 27 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

| Item no. | Mercer (2016) [90] | Miranda (2022) [91] | Panagioti (2018) [92] | Salari (2022) [95] | Thorn (CUA) (2020) [96] | Thorn (CCA) (2020) [96] | Vila (2015) [93] | Zimmerman (2017) [94] |
|---|---|---|---|---|---|---|---|---|
| 28 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

CCA, cost-consequence analysis; CHEERS 2022, Consolidated Health Economic Evaluation Reporting Standards 2022; CUA, cost-utility analysis; NA, not applicable; No, number.

**Appendix A.7: Total quality score of each economic evaluation based on QHES.**

| Lead author (publication date) | QHES questions | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4[a] | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | Q16 | Total |
| **Care coordination plus self-management support interventions** | | | | | | | | | | | | | | | | | |
| Kari (2022)[87] | 7 | 2 | 8 | 1 | 4.5 | 6 | 5 | 5 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 86.5 |
| Lanzeta (2016)[88] | 7 | 0 | 8 | 1 | 9 | 6 | 5 | 3 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 87 |
| Mercer (2016)[90] | 7 | 4 | 8 | 1 | 4.5 | 6 | 5 | 5 | 6 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 86.5 |
| Thorn (CUA) (2020)[96] | 7 | 4 | 8 | 1 | 4.5 | 6 | 5 | 7 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 90.5 |
| Thorn (CCA) (2020)[96] | 7 | 4 | 8 | 1 | NA | 6 | 5 | 7 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 86 |
| Zimmerman (2017)[94] | 7 | 2 | 4 | 1 | 0 | 6 | 5 | 3 | 8 | 0 | 0 | 8 | 7 | 3 | 8 | 3 | 64 |
| Average | | | | | | | | | | | | | | | | | 83.4 |
| **Coordinated care interventions** | | | | | | | | | | | | | | | | | |
| Ekdahl (2015)[82] | 7 | 0 | 8 | 1 | 4.5 | NA | 5 | 3 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 76.5 |
| Ekdahl (2016)[83] | 7 | 0 | 8 | 1 | 0 | NA | 5 | 3 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 72 |
| Evans (2021)[84f] | 7 | 0 | 8 | 1 | 9 | 6 | 5 | 3 | 6 | 4 | 0 | 0 | 7 | 3 | 8 | 3 | 70 |
| Gayot (2022)[85] | 7 | 2 | 8 | 1 | 4.5 | 6 | 5 | 3 | 6 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 82.5 |
| Lundqvist (2018)[89] | 7 | 2 | 8 | 1 | 9 | 6 | 5 | 5 | 6 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 89 |
| Vila (2015)[93] | 7 | 0 | 4 | 1 | NA | 6 | 5 | 3 | 8 | 4 | 7 | 4 | 7 | 3 | 8 | 3 | 70 |
| Average | | | | | | | | | | | | | | | | | 76.7 |

| Lead author (publication date) | QHES questions | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Self-management support interventions** | | | | | | | | | | | | | | | | | |
| Basu (2015)[81] | 7 | 0 | 4 | 1 | 0 | 6 | 5 | 3 | 8 | 6 | 7 | 8 | 7 | 3 | 8 | 3 | 75 |
| Gillespie (2022)[86] | 7 | 2 | 8 | 1 | 9 | 6 | 5 | 3 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 89 |
| Miranda (2022)[91] | 7 | 2 | 8 | 1 | 4.5 | 6 | 5 | 3 | 8 | 6 | 7 | 8 | 7 | 3 | 8 | 3 | 86.5 |
| Panagioti (2018)[92] | 7 | 2 | 6 | 1 | 9 | 6 | 5 | 7 | 8 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 91 |
| Average | | | | | | | | | | | | | | | | | 85.4 |
| **Medicines management** | | | | | | | | | | | | | | | | | |
| Salari (2022)[95] | 7 | 2 | 8 | 1 | 9 | 6 | 5 | 3 | 6 | 4 | 7 | 8 | 7 | 3 | 8 | 3 | 87 |
| Average for all studies | 7 | 1.5 | 7.1 | 1 | 5.1 | 6 | 5 | 3.9 | 7.4 | 4 | 6.2 | 7.3 | 7 | 0.6 | 8 | 3 | 81.7 |

CCA indicates cost-consequence analysis; CUA, cost-utility analysis; NA, not applicable; QHES, quality of health economic studies.

[a] A point was lost only if a subgroup analysis was completed, and subgroups were not pre-specified in the methods section or the protocol. If there was no subgroup analysis, a point was assigned automatically

.

# Appendix B. Appendices to Chapter 3

**Appendix B.1: Baseline self-assessment questionnaire.**

| | | |
|---|---|---|
| **Inclusion criteria** | | |
| *Men and women with two or more of the following chronic diseases* | | |
| IHD | | |
| HF | | |
| Diabetes | | |
| CKD | | |
| COPD | | |
| *Daily internet access* | | |
| Home, work or other environment | | |
| Personal computer, data assistant or smartphone | | |
| *Over 19 years of age* | | |
| *Able to read, write and understand English without difficulty* | | |
| **Exclusion criteria** | | |
| *Patients with significant co-morbidities that may interfere with effective management* | | |
| *Patients who have scheduled surgical procedures* | | |
| *Patients who are unable to provide informed consent* | | |
| **Gender** | **Date of birth**: mm/dd/yyyy | |
| Male | | |
| Female | | |
| **Medical history** | | |
| *Does the patient attend clinics for any of their following conditions?* | | |
| **Clinics** | | |
| Condition | City | Number of times per year |
| HF | | |
| IHD | | |
| Diabetes | | |
| COPD | | |
| CKD | | |
| Other | | |
| None | | |
| **Current medications** | | |
| Medication name | Dose | Frequency |
| 1) | | |
| 2) | | |
| 3) | | |
| 4) | | |
| 5) | | |

6)
7)
8)
9)
10)
11)
12)
**Smoking status**
Never
Former
Current
**Alcohol consumption**
Never/<1 per week
1-5 per week
6-10 per week
>10 per week
**Recent laboratory tests (<90 days)**
**Diagnostic tests**
Angiogram
CT Angiogram
Angioplasty
MIBI
Bruce EST
Echocardiogram
Chest Ex-ray
**Laboratory tests**
*Diabetes*
HgbA1c
Fasting Glucose
GTT
*Kidney disease*
E+, Ca, Mg & Phosphors
GFR
BUN & Creatinine
*HF*
BNP
PRO NT BNP
Hg
*COPD*
Arterial Blood Gas or 02 Saturation
FEV
*IHD*
Tropinin
Lipid Panel
**Internet use**
*How is your household computer connected to the Internet? (Mark all that apply)*
Telephone line connected to a computer
Cable line connected to a computer

Connected through television
Wireless
Other
*Is your household Internet connection a "High Speed" connection?*
Yes
No
*From what location do you typically use the Internet?*
Home
Work
Library
Relative's home
Friend's/neighbours home
Other
*How often do you use the internet?*
Daily
Once a week
More than once a week
Once a month
Never
*What do you use the Internet for? (Mark all that apply)*
General browsing/Information search
E-mail/hotmail
Search for medical/health related information
Personal use (e.g., banking, music, game, purchase of goods & services)
Other
*Do you require any help when using a computer? (ie: due to physical limitations)*
Yes
No
**Social demographics**
*What is your maximum level of education?*
Less than high school
High school graduate (or equivalent)
Some post-secondary education
Post-secondary degree or diploma
Post graduate education
Other
*What is your current employment status?*
Full-time job
Full-time homemaker
Part-time job
Unemployed
Retired

| |
|---|
| Other |
| *What is your total pre-tax household income?* |
| Less than $20,000 |
| $20,000 to $29,999 |
| $30,000 to $39,999 |
| $40,000 to $49,999 |
| $50,000 to $60,000 |
| More than $60,000 |
| Other |
| *What is your current marital status?* |
| Single |
| Married |
| Divorced |
| Common-law |
| Widowed |
| Other |

BNP indicates brain natriuretic peptide; BUN, blood urea nitrogen; CA, calcium; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; CKD, chronic kidney disease; FEV, forced expiratory volume; GFR, glomerular filtration rate; GTT, glucose tolerance test, HF, heart failure; HG, mercury; HGB, hemoglobin; IHD, ischemic heart disease; MG, magnesium; MIBI, Myocardial perfusion imaging; NP, natriuretic peptide.

## Appendix B.2: One year follow-up self-assessment questionnaire.

| | | |
|---|---|---|
| *Has the patient joined a clinic for any of their conditions in the previous year?* | | |
| **Clinics** | | |
| Condition | City | Number of times per year |
| HF | | |
| IHD | | |
| Diabetes | | |
| COPD | | |
| CKD | | |
| Other | | |
| None | | |
| **Hospital utilization in the last year** | | |
| Has the participant been admitted to any hospitals/ERs for any reason in the previous year? | | |
| No | | |
| Yes | | |
| 1) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission | | |
| 2) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 3) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 4) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 5) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 6) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| *Did any of the following events/new diagnoses occur in the previous year?* | | |
| a) MI/Heart attack | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| b) Angina | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| c) HF | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| d) Other heart disease | | |
| Yes | Date of event: | Date of admission: |

| | | |
|---|---|---|
| No | | |
| e) COPD | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| f) Diabetes | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| g) CKD | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| h) Stroke | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| i) Cancer | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| j) Other diagnoses | Date of diagnosis: | |
| k) Other diagnoses | Date of diagnosis: | |
| l) Other diagnoses | Date of diagnosis: | |
| m) Other diagnoses | Date of diagnosis: | |
| n) Other event | Date of event: | |
| o) Other event | Date of event: | |
| p) Other event | Date of event: | |
| q) Other event | Date of event: | |

COPD indicates chronic obstructive pulmonary disease; CKD, chronic kidney disease; HF, heart failure; IHD, ischemic heart disease.

**Appendix B.3: Two-year follow-up self-assessment questionnaire.**

| | | |
|---|---|---|
| *Has the patient joined a clinic for any of their conditions in the previous year?* | | |
| **Clinics** | | |
| Condition | City | Number of times per year |
| HF | | |
| IHD | | |
| Diabetes | | |
| COPD | | |
| CKD | | |
| Other | | |
| None | | |
| **Current medications or vitamins** | | |
| Name | Dose | Frequency |
| 1) | | |
| 2) | | |
| 3) | | |
| 4) | | |
| 5) | | |
| 6) | | |
| 7) | | |
| 8) | | |
| 9) | | |
| 10) | | |
| 11) | | |
| 12) | | |
| **Smoking status** | | |
| Never | | |
| Former | | |
| Current | | |
| **Alcohol consumption** | | |
| Never/<1 per week | | |
| 1-5 per week | | |
| 6-10 per week | | |
| >10 per week | | |
| **Recent laboratory tests (<90 days)** | | |
| **Diagnostic tests** | | |
| Angiogram | | |
| CT Angiogram | | |
| Angioplasty | | |
| MIBI | | |
| Bruce EST | | |
| Echocardiogram | | |
| Chest Ex-ray | | |
| **Laboratory tests** | | |
| *Diabetes* | | |
| HgbA1c | | |
| Fasting Glucose | | |
| GTT | | |

| | | |
|---|---|---|
| *Kidney disease* | | |
| E+, Ca, Mg & Phosphors | | |
| GFR | | |
| BUN & Creatinine | | |
| *HF* | | |
| BNP | | |
| PRO NT BNP | | |
| Hg | | |
| *COPD* | | |
| Arterial Blood Gas or 02 Saturation | | |
| FEV | | |
| *IHD* | | |
| Tropinin | | |
| Lipid Panel | | |
| **Hospital utilization in the last year** | | |
| Has the participant been admitted to any hospitals/ERs for any reason in the previous year? | | |
| No | | |
| Yes | | |
| 1) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission | | |
| 2) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 3) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 4) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 5) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| 6) Hospital/ER: | Admission date: | |
| # days in hospital: | | |
| Reason for admission: | | |
| *Did any of the following events/new diagnoses occur in the previous year?* | | |
| a) MI/Heart attack | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| b) Angina | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| c) HF | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| d) Other heart disease | | |
| Yes | Date of event: | Date of admission: |

| | | |
|---|---|---|
| No | | |
| e) COPD | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| f) Diabetes | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| g) CKD | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| h) Stroke | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| i) Cancer | | |
| Yes | Date of event: | Date of admission: |
| No | | |
| j) Other diagnoses | Date of diagnosis: | |
| k) Other diagnoses | Date of diagnosis: | |
| l) Other diagnoses | Date of diagnosis: | |
| m) Other diagnoses | Date of diagnosis: | |
| n) Other event | Date of event: | |
| o) Other event | Date of event: | |
| p) Other event | Date of event: | |
| q) Other event | Date of event: | |

BNP indicates brain natriuretic peptide; BUN, blood urea nitrogen; CA, calcium; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; CKD, chronic kidney disease; FEV, forced expiratory volume; GFR, glomerular filtration rate; GTT, glucose tolerance test, HF, heart failure; HG, mercury; HGB, hemoglobin; IHD, ischemic heart disease; MG, magnesium; MIBI, Myocardial perfusion imaging; NP, natriuretic peptide.

**Appendix B.4: Comparison of baseline characteristics for patients lost to follow-up and those who remained in the study throughout. Values are numbers (percentages) unless stated otherwise.[a]**

| Characteristic | Not lost to follow-up (n=210) | Lost to follow-up (n=19) | *p* value[b] |
|---|---|---|---|
| Age, mean (sd) | 70.2 (9.04) | 73.5 (10.26) | 0.135 |
| Sex | | | |
| Female | 80 (38.10) | 8 (42.11) | 0.731 |
| Male | 130 (61.90) | 11 (57.89) | |
| Chronic disease | | | |
| Ischemic heart disease | 122 (58.10) | 13 (68.42) | 0.381 |
| Chronic heart failure | 39 (18.57) | 11 (57.89) | < 0.001 |
| Diabetes | 153 (72.86) | 11 (57.89) | 0.166 |
| Chronic kidney disease | 123 (58.57) | 10 (52.63) | 0.615 |
| COPD | 63 (30.00) | 7 (36.84) | 0.535 |
| No. of chronic diseases, mean (sd) | 2.38 (0.63) | 2.74 (0.73) | 0.021 |
| Educational level | | | |
| Did not finish high school | 42 (20.00) | 0 (0) | 0.704 |
| High school or equivalent | 56 (26.67) | 12 (63.16) | |
| Some post-secondary education | 50 (23.81) | 3 (15.79) | |
| Post-secondary degree | 46 (21.90) | 4 (21.05) | |
| Postgraduate degree | 11 (5.24) | 0 (0) | |
| Other[c] | 5 (2.38) | 0 (0) | |
| Pre-tax household income | | | |
| Less than $20,000 | 28 (13.59) | 2 (11.76) | 0.354 |
| $20,000 to $29,999 | 34 (16.50) | 8 (47.06) | |
| $30,000 to $39,999 | 34 (13.76) | 2 (11.76) | |
| $40,000 to $49,999 | 28 (13.59) | 1 (5.88) | |
| $50,000 to $59,999 | 26 (12.62) | 1 (5.88) | |
| More than $59,999 | 56 (27.18) | 3 (17.65) | |
| Current employment status | | | |
| Full time | 21 (10.05) | 1 (5.26) | 0.273 |
| Part time | 6 (2.87) | 0 (0) | |
| Unemployed | 4 (1.91) | 2 (10.53) | |
| Retired | 158 (75.60) | 15 (78.95) | |
| Other[c] | 20 (9.57) | 1 (5.26) | |
| Marital status | | | |
| Single | 8 (3.81) | 0 (0) | 0.688 |

| Characteristic | Not lost to follow-up (n=210) | Lost to follow-up (n=19) | *p* value[b] |
|---|---|---|---|
| Married | 30 (14.29) | 4 (21.05) | |
| Divorced | 15 (7.14) | 2 (10.53) | |
| Widowed | 140 (66.67) | 13 (68.42) | |
| Common law | 12 (5.71) | 0 (0) | |
| Other[c] | 5 (2.38) | 0 (0) | |
| Frequency of internet usage | | | |
| Daily | 155 (73.81) | 11 (57.89) | |
| More than once a week | 21 (10.00) | 2 (10.53) | |
| Once a week | 14 (6.67) | 4 (21.05) | 0.134 |
| Once a month | 5 (2.38) | 0 (0) | |
| Never | 15 (7.14) | 2 (10.53) | |
| eHEALS, mean (sd) | 30.90 (8.30) | 32.37 (9.86) | 0.467 |
| CES-D, mean (sd) | 12.17 (10.51) | 13.58 (13.73) | 0.586 |
| Smoking status | | | |
| Current | 17 (8.25) | 2 (31.58) | |
| Former | 133 (64.56) | 11 (10.53) | 0.840 |
| Never | 56 (27.18) | 6 (57.89) | |
| Alcohol consumption | | | |
| never/<1 per week | 128 (61.00) | 5 (26.30) | |
| 1-5 per week | 47 (22.40) | 7 (36.80) | 0.003 |
| 6-10 per week | 22 (10.50) | 4 (21.10) | |
| >10 per week | 13 (6.20) | 3 (15.80) | |

CES-D indicates Centre for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; eHEALS, eHealth Literacy Scale; n, number; No., number; sd, standard deviation.

[a] With the exception of the 'Chronic disease' question (where an inclusion criterion was for patients to have two or more of the listed chronic diseases), all questions had mutually-exclusive response options. Numbers do not always sum to the respective totals because of missing data.

[b] Details of the statistical tests used for the different variables (continuous and categorical) are provided on page 64. P values are reported to three decimal places.

[c] 'Other' comprises responses that could not be categorized in one of the response options listed in the baseline assessment questionnaire.

**Appendix B.5: Comparison of baseline characteristics for patients recruited before and after the addition of the EQ-5D-5L as a study outcome. Values are numbers (percentages) unless stated otherwise.[a]**

| Characteristic | Early recruitment (n=109) | Late recruitment (n=120) | *p* value[b] |
|---|---|---|---|
| Age, mean (sd) | 70.9 (8.64) | 70.1 (9.64) | 0.512 |
| Sex | | | |
| Female | 45 (41.28) | 43 (35.83) | 0.397 |
| Male | 64 (58.72) | 77 (64.17) | |
| Chronic disease | | | |
| Ischemic heart disease | 68 (62.39) | 67 (55.83) | 0.314 |
| Chronic heart failure | 24 (22.02) | 26 (21.67) | 0.949 |
| Diabetes | 79 (72.48) | 85 (70.83) | 0.783 |
| Chronic kidney disease | 57 (52.29) | 76 (63.33) | 0.091 |
| COPD | 34 (31.19) | 36 (30.00) | 0.845 |
| No. of chronic diseases, mean (sd) | 2.40 (0.61) | 2.42 (0.68) | 0.880 |
| Educational level | | | |
| Did not finish high school | 18 (16.51) | 24 (20.00) | 0.005 |
| High school or equivalent | 33 (30.28) | 35 (29.17) | |
| Some post-secondary education | 27 (24.77) | 26 (21.67) | |
| Post-secondary degree | 22 (20.18) | 28 (23.33) | |
| Postgraduate degree | 10 (9.17) | 1 (0.83) | |
| Other[c] | 0 (0.00) | 5 (4.17) | |
| Pre-tax household income | | | |
| Less than $20,000 | 15 (13.76) | 15 (12.50) | 0.074 |
| $20,000 to $29,999 | 25 (22.94) | 17 (14.17) | |
| $30,000 to $39,999 | 15 (13.76) | 21 (17.50) | |
| $40,000 to $49,999 | 12 (11.01) | 17 (14.17) | |
| $50,000 to $59,999 | 12 (11.01) | 15 (12.50) | |
| More than $59,999 | 25 (22.94) | 34 (28.33) | |
| Current employment status | | | |
| Full time | 11 (10.09) | 11 (9.17) | 0.882 |
| Part time | 3 (2.75) | 3 (2.50) | |
| Unemployed | 3 (2.75) | 3 (2.50) | |
| Retired | 82 (75.23) | 91 (75.83) | |
| Other[c] | 9 (8.26) | 12 (10.00) | |
| Marital status | | | |

| Characteristic | Early recruitment (n=109) | Late recruitment (n=120) | *p* value[b] |
|---|---|---|---|
| Single | 8 (7.34) | 4 (3.33) | |
| Married | 64 (58.72) | 89 (74.17) | |
| Divorced | 10 (9.17) | 7 (5.83) | 0.144 |
| Widowed | 19 (17.43) | 15 (12.50) | |
| Common law | 6 (5.50) | 2 (1.67) | |
| Other[c] | 2 (1.83) | 3 (2.50) | |
| Frequency of internet usage | | | |
| Daily | 76 (69.7) | 90 (75.0) | |
| More than once a week | 13 (11.9) | 10 (8.30) | |
| Once a week | 9 (8.30) | 9 (7.50) | 0.415 |
| Once a month | 2 (1.80) | 3 (2.50) | |
| Never | 9 (8.30) | 8 (6.70) | |
| eHEALS, mean (sd) | 31.33 (8.83) | 30.73 (8.07) | 0.594 |
| CES-D, mean (sd) | 12.72 (10.34) | 11.88 (11.20) | 0.556 |
| Smoking status | | | |
| Current | 9 (8.26) | 10 (8.55) | |
| Former | 67 (61.47) | 79 (65.83) | 0.623 |
| Never | 32 (29.36) | 28 (23.33) | |
| Alcohol consumption | | | |
| never/<1 per week | 55 (50.50) | 78 (65.00) | |
| 1-5 per week | 31 (28.40) | 23 (19.20) | 0.052 |
| 6-10 per week | 17 (15.60) | 9 (7.50) | |
| >10 per week | 6 (5.50) | 10 (8.30) | |

CES-D indicates Centre for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; eHEALS, eHealth Literacy Scale; iCDM, internet chronic disease management; n, number; No., number; sd, standard deviation.

[a] With the exception of the 'Chronic disease' question (where an inclusion criterion was for patients to have two or more of the listed chronic diseases), all questions had mutually-exclusive response options. Numbers do not always sum to the respective totals because of missing data.

[b] Details of the statistical tests used for the different variables (continuous and categorical) are provided on page 64. P values are reported to three decimal places.

[c] 'Other' comprises responses that could not be categorized in one of the response options listed in the baseline assessment questionnaire.

**Appendix B.6: Resource use per patient over 24 months, by treatment group. Values are mean (standard deviation) number of visits for observed cases unless otherwise stated.**

| Item of resource | n | iCDM | n | Usual care |
|---|---|---|---|---|
| **B to 12M** | | | | |
| *Inpatient services* | | | | |
| Hospital visit | 111 | 0.43 (0.87) | 109 | 0.51 (1.01) |
| *Outpatient services* | | | | |
| ED visit | 111 | 0.40 (0.80) | 109 | 0.49 (0.89) |
| Clinic visit | 111 | 3.05 (18.10) | 109 | 0.21 (0.86) |
| **12M to 24M** | | | | |
| *Inpatient services* | | | | |
| Hospital visit | 106 | 0.41 (0.95) | 104 | 0.45 (0.80) |
| *Outpatient services* | | | | |
| ED visit | 106 | 0.49 (1.11) | 104 | 0.36 (0.70) |
| Clinic visit | 106 | 0.63 (3.27) | 104 | 0.90 (4.06) |
| **B to 24M** | | | | |
| *Inpatient services* | | | | |
| Hospital visit | 111 | 0.82 (1.44) | 109 | 0.95 (1.40) |
| *Outpatient services* | | | | |
| ED visit | 111 | 0.86 (1.49) | 109 | 0.83 (1.32) |
| Clinic visit | 111 | 3.66 (18.30) | 109 | 1.07 (4.09) |

B, baseline; ED, emergency department; iCDM, internet chronic disease management; M, months; n, number.

**Appendix B.7: Healthcare costs ($) per patient over 24 months, by treatment group, for the observed case data set.**

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| **B to 12M** | | | | | |
| *Inpatient services* | | | | | |
| Hospital visit | 111 | 4724.12 (9461.07) | 109 | 6982.48 (18342.54) | -2240.358 (-6108.60 to 1627.89; 0.255) |
| *Outpatient services* | | | | | |
| ED visit | 111 | 139.01 (280.86) | 109 | 173.73 (311.56) | -34.723 (-113.51 to 44.07; 0.386) |
| MSP for ED visit | 111 | 36.79 (74.65) | 109 | 47.62 (93.25) | -10.826 (-33.25 to 11.60; 0.342) |
| Clinic visit | 111 | 1010.22 (5988.00) | 109 | 69.80 (284.95) | 940.422 (-191.29 to 2072.13; 0.103) |
| Total costs | 111 | 5928..14 (11023.94) | 109 | 7273.62 (18411.95) | -1345.48 (-5369.62 to 2678.65; 0.511) |
| **12M to 24M** | | | | | |
| *Inpatient services* | | | | | |
| Hospital visit | 106 | 4106.90 (10329.45) | 104 | 5697.17 (11200.58) | -1427.792 (-4520.65 to 1340.11; 0.286) |
| *Outpatient services* | | | | | |
| ED visit | 106 | 172.03 (387.93) | 104 | 128.13 (244.61) | 43.899 (-44.52 to 132.32; 0.329) |
| MSP for ED visit | 106 | 36.82 (85.62) | 104 | 29.69 (61.86) | 7.129 (-13.23 to 27.48; 0.491) |
| Clinic visit | 106 | 209.08 (1082.56) | 104 | 298.97 (1334.24) | -89.896 (-421.63 to 241.84; 0.594) |
| Total costs | 106 | 4524.83 (10444.60) | 104 | 6153.96 (11496.71) | -1629.138 (-4616.27 to 1357.99; 0.284) |
| **B to 24M** | | | | | |
| *Inpatient services* | | | | | |

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| Hospital visit | 111 | 8548.96 (14890.40) | 109 | 12258.83 (23084.48) | -3709.869 (-8862.48 to 1442.75; 0.157) |
| *Outpatient services* | | | | | |
| ED visit | 111 | 298.47 (511.72) | 109 | 292.40 (455.15) | 6.071 (-122.70 to 134.84; 0.926) |
| MSP for ED visit | 111 | 70.92 (124.40) | 109 | 75.11 (121.97) | -4.194 (-36.94 to 28.55; 0.801) |
| Clinic visit | 111 | 1204.02 (6048.66) | 109 | 346.69 (1315.51) | 857.334 (-310.78 to 2025.45; 0.151) |
| Total costs | 111 | 10122.37 (15867.79) | 109 | 12973.03 (23374.20) | -2850.658 (-8150.84 to 2449.52; 0.290) |

B, baseline; ED, emergency department; iCDM, internet chronic disease management; MSP, medical services plan; M, months; n, number.

[a] Differences in mean values were calculated as values for patients receiving iCDM minus values for patients receiving usual care.

**Appendix B.8: Medications and vitamins used, laboratory tests, and diagnostic tests performed per patient for observed cases at baseline and 24 months, by treatment group.**

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| **Baseline** | | | | | |
| *Medications* | | | | | |
| Cardiovascular agents | 116 | 2.83 (1.46) | 113 | 3.15 (1.55) | -0.323 (-0.71 to 0.07; 0.106) |
| Gastrointestinal agents | 116 | 0.45 (0.64) | 113 | 0.47 (0.58) | -0.021 (-0.18 to 0.14; 0.798) |
| Blood glucose regulators | 116 | 0.83 (0.90) | 113 | 0.80 (0.97) | 0.031 (-0.21 to 0.28; 0.802) |
| Blood products and modifiers | 116 | 0.85 (0.62) | 113 | 0.80 (0.66) | 0.057 (-0.11 to 0.22; 0.501) |
| Respiratory tract agents | 116 | 0.59 (0.99) | 113 | 0.49 (0.96) | 0.108 (-0.15 to 0.36; 0.401) |
| Analgesics | 116 | 0.22 (0.49) | 113 | 0.31 (0.58) | -0.094 (-0.23 to 0.05; 0.187) |
| Antidepressants | 116 | 0.16 (0.39) | 113 | 0.30 (0.63) | -0.137 (-0.27 to 0.00; 0.048) |
| Antigout agents | 116 | 0.11 (0.34) | 113 | 0.17 (0.44) | -0.056 (-0.16 to 0.05; 0.283) |
| Hormonal agents | 116 | 0.25 (0.45) | 113 | 0.21 (0.43) | 0.038 (-0.08 to 0.15; 0.522) |
| Genitourinary Agents | 116 | 0.20 (0.53) | 113 | 0.16 (0.43) | 0.039 (-0.09 to 0.17; 0.544) |
| Other | 116 | 0.66 (0.96) | 113 | 0.78 (1.12) | -0.115 (-0.39 to 0.16; 0.413) |
| *Vitamins* | 116 | 1.13 (1.51) | 113 | 1.28 (1.80) | -0.154 (-0.59 to 0.28; 0.483) |
| *Laboratory tests[b]* | | | | | |
| Hgb A1c | 116 | 0.09 (0.28) | 113 | 0.08 (0.27) | 0.007 (-0.07 to 0.08; 0.858) |

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| Fasting Glucose | 116 | 0.06 (0.24) | 113 | 0.04 (0.21) | 0.016 (-0.04 to 0.07; 0.587) |
| GTT | 116 | 0.01 (0.09) | 113 | 0.01 (0.09) | 0.000 (-0.03 to 0.02; 0.985) |
| E+, Ca, Mg & Phosphors | 116 | 0.04 (0.20) | 113 | 0.08 (0.27) | -0.037 (-0.10 to 0.03; 0.250) |
| GFR | 116 | 0.11 (0.32) | 113 | 0.09 (0.29) | 0.024 (-0.06 to 0.10; 0.555) |
| BUN & Creatinine | 116 | 0.09 (0.29) | 113 | 0.12 (0.32) | -0.020 (-0.10 to 0.06; 0.619) |
| BNP | 116 | 0.01 (0.09) | 113 | 0.00 (0.00) | 0.009 (-0.01 to 0.03; 0.325) |
| Pro NT BNP | 116 | 0.01 (0.09) | 113 | 0.00 (0.00) | 0.009 (-0.01 to 0.03; 0.325) |
| Hg | 116 | 0.01 (0.09) | 113 | 0.00 (0.00) | 0.009 (-0.01 to 0.03; 0.325) |
| O2 Saturation | 116 | 0.00 (0.00) | 113 | 0.00 (0.00) | / |
| Fev | 116 | 0.01 (0.09) | 113 | 0.00 (0.00) | 0.009 (-0.10 to 0.03; 0.325) |
| Tropinin | 116 | 0.01 (0.09) | 113 | 0.00 (0.00) | 0.009 (-0.10 to 0.03; 0.325) |
| Lipid Panel | 116 | 0.08 (0.27) | 113 | 0.06 (0.24) | 0.016 (-0.05 to 0.08; 0.644) |
| *Diagnostic tests*[b] | | | | | |
| Angiogram | 116 | 0.01 (0.09) | 113 | 0.01 (0.09) | 0.000 (-0.03 to 0.02; 0.985) |
| CT Angiogram | 116 | 0.00 (0.00) | 113 | 0.01 (0.09) | -0.009 (-0.03 to 0.01; 0.312) |
| Angioplasty | 116 | 0.00 (0.00) | 113 | 0.00 (0.00) | / |
| MIBI | 116 | 0.00 (0.00) | 113 | 0.02 (0.13) | -0.018 (-0.04 to 0.01; 0.151) |
| Bruce EST | 116 | 0.00 (0.00) | 113 | 0.00 (0.00) | / |
| Echocardiogram | 116 | 0.05 (0.22) | 113 | 0.02 (0.13) | 0.034 (-0.01 to 0.08; 0.162) |

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| Chest Ex-ray | 116 | 0.04 (0.20) | 113 | 0.00 (0.00) | 0.043 (0.01 to 0.08; 0.026) |
| **24-month follow-up** | | | | | |
| *Medications* | | | | | |
| Cardiovascular agents | 106 | 2.80 (1.48) | 103 | 2.76 (1.59) | 0.045 (-0.38 to 0.46; 0.834) |
| Gastrointestinal agents | 106 | 0.48 (0.71) | 103 | 0.43 (0.60) | 0.054 (-0.13 to 0.23; 0.554) |
| Blood glucose regulators | 106 | 0.85 (1.01) | 103 | 0.75 (0.95) | 0.101 (-0.17 to 0.37; 0.455) |
| Blood products and modifiers | 106 | 0.80 (0.62) | 103 | 0.80 (0.76) | 0.006 (-0.17 to 0.21; 0.952) |
| Respiratory tract agents | 106 | 0.39 (0.81) | 103 | 0.49 (0.94) | -0.099 (-0.34 to 0.14; 0.417) |
| Analgesics | 106 | 0.25 (0.60) | 103 | 0.25 (0.56) | 0.002 (-0.16 to 0.16; 0.977) |
| Antidepressants | 106 | 0.22 (0.57) | 103 | 0.28 (0.57) | -0.065 (-0.22 to 0.09; 0.412) |
| Antigout agents | 106 | 0.09 (0.33) | 103 | 0.11 (0.34) | -0.012 (-0.10 to 0.08; 0.787) |
| Hormonal agents | 106 | 0.18 (0.39) | 103 | 0.22 (0.48) | -0.044 (-0.16 to 0.08; 0.467) |
| Genitourinary Agents | 106 | 0.15 (0.43) | 103 | 0.13 (0.33) | 0.025 (-0.08 to 0.13; 0.644) |
| Other | 106 | 0.60 (0.87) | 103 | 0.63 (1.03) | -0.027 (-0.28 to 0.23; 0.836) |
| *Vitamins* | 106 | 1.05 (1.59) | 103 | 1.01 (1.31) | 0.037 (-0.36 to 0.44; 0.853) |
| **24-month follow-up** | | | | | |
| *Laboratory tests*[b] | | | | | |
| Hgb A1c | 106 | 0.23 (0.42) | 103 | 0.20 (0.41) | 0.023 (-0.09 to 0.14; 0.694) |

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| Fasting Glucose | 106 | 0.11 (0.32) | 103 | 0.08 (0.27) | 0.036 (-0.05 to 0.12; 0.385) |
| GTT | 106 | 0.00 (0.00) | 103 | 0.01 (0.10) | -0.010 (-0.03 to 0.01; 0.312) |
| E+, Ca, Mg & Phosphors | 106 | 0.14 (0.35) | 103 | 0.15 (0.35) | -0.004 (-0.10 to 0.09 ; 0.933) |
| GFR | 106 | 0.16 (0.37) | 103 | 0.17 (0.38) | -0.014 (-0.12 to 0.09; 0.782) |
| BUN & Creatinine | 106 | 0.16 (0.37) | 103 | 0.16 (0.36) | 0.005 (-0.10 to 0.11; 0.921) |
| BNP | 106 | 0.00 (0.00) | 103 | 0.00 (0.00) | / |
| Pro NT BNP | 106 | 0.00 (0.00) | 103 | 0.00 (0.00) | / |
| Hg | 106 | 0.00 (0.00) | 103 | 0.00 (0.00) | / |
| O2 Saturation | 106 | 0.03 (0.17) | 103 | 0.01 (0.10) | 0.019 (-0.02 to 0.06; 0.329) |
| Fev | 106 | 0.01 (0.10) | 103 | 0.01 (0.10) | 0.000 (-0.03 to 0.03; 0.984) |
| Tropinin | 106 | 0.02 (0.14) | 103 | 0.00 (0.00) | 0.019 (-0.01 to 0.05; 0.163) |
| Lipid Panel | 106 | 0.09 (0.29) | 103 | 0.08 (0.27) | 0.017 (-0.06 to 0.09; 0.669) |
| *Diagnostic tests*[b] | | | | | |
| Angiogram | 106 | 0.00 (0.00) | 103 | 0.02 (0.14) | -0.019 (-0.05 to 0.01; 0.151) |
| CT Angiogram | 106 | 0.01 (0.10) | 103 | 0.00 (0.00) | 0.009 (-0.01 to 0.03; 0.325) |
| Angioplasty | 106 | 0.00 (0.00) | 103 | 0.00 (0.00) | / |
| MIBI | 106 | 0.01 (0.10) | 103 | 0.01 (0.10) | 0.000 (-0.03 to 0.03; 0.984) |
| Bruce EST | 106 | 0.00 (0.00) | 103 | 0.00 (0.00) | / |
| Echocardiogram | 106 | 0.05 (0.21) | 103 | 0.02 (0.14) | 0.028 (-0.02 to 0.08; 0.267) |

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| Chest Ex-ray | 106 | 0.02 (0.14) | 103 | 0.03 (0.17) | -0.010 (-0.05 to 0.03; 0.630) |

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CA, calcium; COPD, chronic obstructive pulmonary disease; CI, confidence interval; CT, computerized tomography; CKD, chronic kidney disease; FEV, forced expiratory volume; GFR, glomerular filtration rate; GTT, glucose tolerance test, HF, heart failure; HG, mercury; HGB, hemoglobin; iCDM, internet chronic disease management IHD, ischemic heart disease; MG, magnesium; MIBI, Myocardial perfusion imaging; n, number; NP, natriuretic peptide; sd, standard deviation.

[a] Mean difference calculated as the intervention group (iCDM) estimate minus the control group (usual care) estimate.
[b] Laboratory tests and diagnostic tests were performed within 90 days of baseline assessment and 24-month follow-up.

**Appendix B.9: One-way sensitivity analysis for hospital visit cost between iCDM and usual care over 24 months, for the observed case data set.**

| Item of resource | iCDM | | Usual care | | Mean difference[a] |
|---|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) | (95% CI; p value) |
| **Inpatient services** | | | | | |
| *Hospital visit* | | | | | |
| Sensitivity analysis | | | | | |
| B to 12M | 111 | 4561.97 (9154.42) | 109 | 6950.27 (18716.53) | -2388.297 (-6292.76 to 1516.17; 0.229) |
| 12M to 24M | 106 | 4009.82 (10024.56) | 104 | 5484.99 (10879.14) | -1475.167 (-4320.33 to 1370.00; 0.308) |
| B to 24M | 111 | 8278.83 (14335.91) | 109 | 12030.12 (22811.08) | -3751.286 (-8804.28 to 1301.71; 0.145) |
| Base case | | | | | |
| B to 12M | 111 | 4724.12 (9461.07) | 109 | 6982.48 (18342.54) | -2240.358 (-6108.60 to 1627.89; 0.255) |
| 12M to 24M | 106 | 4106.90 (10329.45) | 104 | 5697.17 (11200.58) | -1427.792 (-4520.65 to 1340.11; 0.286) |
| B to 24M | 111 | 8548.96 (14890.40) | 109 | 12258.83 (23084.48) | -3709.869 (-8862.48 to 1442.75; 0.157) |

B, baseline; iCDM indicates internet chronic disease management; M, months; n, number.

[a] Differences in mean values were calculated as values for patients receiving iCDM minus values for patients receiving usual care.