Improving the Estimation of Cost-of-Illness in Rheumatoid Arthritis

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Abstract

Cost-of-illness (COI) studies measure the economic burden of a disease and estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated. Estimates of the COI can help appropriately target specific problems and policies on a disease in policy agenda setting. COI studies are particularly useful for chronic diseases that impact heavily on health expenditures and productivity loss for the whole society. It is essential for policymakers to know where costs are incurred. Consequently, appropriate interventions can be implemented and prioritised. Over the past two decades, the accumulation of coexisting long-term conditions within an individual has been confirmed as the best predictor of sustained high costs. It is now an established priority for both research and clinical practice owing to the high prevalence of coexisting diseases among patients, particularly with ageing populations. Because of this shift in how we approach chronic diseases in medical research, it is pertinent that we also think about how this impacts the way we look at COI.

On the other hand, inconsistencies in the designs and methodologies that COI studies are conducted and a lack of transparency in reporting have made interpretation and comparison difficult and have limited the usefulness of results in health decision making. Variations include data sources, perspectives, cost components, and costing approaches. On the other hand, while standardisation of methodology through the implementation of guidelines is becoming increasingly important, some flexibility may be required for diseases or different contexts with unique characteristics to be adequately described.

Rheumatoid arthritis (RA), as one of the most common chronic diseases, is a leading cause of work disability worldwide. Although numerous COI studies have attempted to quantify the economic burden of RA, the cost estimates vary substantially due to different

methodological approaches, perspectives and settings. This thesis aims to improve the estimation of COI. To explore the differences in estimating COI, two case studies were developed in diverse contexts: Scotland and Tanzania. Both studies were complementary to each other in terms of different approaches and contexts to estimating COI. The former was in a high-income country, using secondary data analysis from a RA inception cohort linked to routinely collected health records to estimate the COI. In contrast, the latter was in a low- and middle-income country with limited treatment options. Due to the absence of routinely collected health data and the availability of screening tools for RA, a widening criterion of musculoskeletal (MSK) disorders was adopted. A context-specific questionnaire was developed to collect primary data to estimate the COI of MSK in Tanzania.

This thesis confirms the need for improved estimation of COI studies. Good quality COI studies are not easy to do. Current evidence shows a lack of consistency in taking into account indirect costs, resulting in underestimating COI in RA. Moreover, indirect costs need more attention, with improvements in terms of data collection and costing approaches. Health conditions are complex and multi-dimensional, especially when the way we look at them have evolved over time. It is becoming clear that context is also an influencing factor in estimating COI. These complexities need to be considered in COI. While many systematic reviews for COI studies have urged the need to increase comparability, it is more crucial to be transparent in reporting contexts and methodological clarity, including identifying, measuring, and valuing COI.

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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

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Papers and presentations

The following publications, working papers and presentations were developed as part of this thesis:

Published paper

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Working paper (being drafted for submission)

Hsieh P-H, Geue, C, Wu O, McIntosh E, Siebert S. How does multiple long-term conditions impact on the cost-of illness in people with early rheumatoid arthritis? (under review)

Presentations

How Does Multimorbidity Impact on the Cost-of-Illness in Patients with Rheumatoid Arthritis? Results from the SERA study. Health Technology Assessment International Annual Meeting (virtual), Manchester, UK, June 2021. (shortlisted for the best student oral presentation award)

How does multimorbidity impact on the direct and indirect costs in patients with rheumatoid arthritis? European Alliance of Associations for Rheumatology Congress (virtual), Paris, France, June 2021.

Impact on Costs in Patients with early Rheumatoid Arthritis. Poster presentation. ISPOR Asia Pacific Virtual Conference. September 2020.

Impact of Biologics on Rheumatoid Arthritis: How Have Costs Evolved? Oral Presentation. Health Technology Assessment International (HTAi) Annual Meeting, Cologne, Germany, June 2019.

The Evolving Cost of Illness of Rheumatoid Arthritis: A Systematic Review. Poster presentation. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Asia Pacific Congress, Tokyo, Japan, September 2018.

The Evolving Drug Expenses and Healthcare Costs of Rheumatoid Arthritis: A Systematic Review. Poster presentation. International Pharmaceutical Federation (FIP) World Congress, Glasgow, UK, September 2018.

Abbreviations

BNF: British National Formulary
CAQ: Cost Assessment Questionnaire
CCI: Charlson Comorbidity Index
CHEERS: Consolidated Health Economics Evaluation Reporting Standards
CHI: Community Health Index
CHOICE: CHOosing Interventions that are Cost-Effective
CI: confidence interval
COI: cost of illness
CPI: consumer price index
CVD: cardiovascular disease
DALY: disability-adjusted life year
DAS: Disease Activity Score
DMARD: Disease Modified Anti-Rheumatic Drug
EQ-5D: EuroQol 5 Dimensions
FCA: Friction Cost Approach
GALS: Gait Arms Legs Spine
GDP: Gross Domestic Product
GHRG: Global Health Research Group
GI: gastrointestinal
GLM: Generalised Linear Model
HAQ-DI: Health Assessment Questionnaire – Disability Index
HCA: Human Capital Approach
HIC: high-income countries
HLQ: Health and Labour Questionnaire
HPQ: Health and Work Performance Questionnaire
HRQoL: Health Related Quality of Life
HTA: Health Technology Assessment
ICER: incremental cost-effectiveness ratio
ICD-10: International Classification of Diseases, Tenth Revision
ISD: Information Service Division
LIC: low-income countries
LMIC: low- and middle-income countries
MSK: musculoskeletal disorder
NCD: non-communicable diseases
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
NSAID: non-steroidal anti-inflammatory drug
OOP: out-of-pocket
ODK: Open Data Kit
QALY: quality-adjusted life year
QOL: health related quality of life
PRIMA: Preferred Reporting Items for Systematic Review and Meta-analyses

PIS: Prescription Information System
RA: rheumatoid arthritis
RCT: randomised controlled trial
REMS: Regional Examination of the musculoskeletal system
SERA: Scottish Early Rheumatoid Arthritis
SD: standard deviation
SES: socioeconomic status
SIMD: Scottish Index of Multiple Deprivation
SMR: Scottish Morbidity Records
SWIM: Synthesis without Meta-Analysis
TNF: tumour necrosis factor
T2T: treat to target
UK: United Kingdom
USD: US dollars
VAS: visual analogue scale
WHO: World Health Organisation
WPAI: Work Productivity and Activity Impairment Questionnaire

CHAPTER 1. CONTEXT AND RATIONALE

1.1 Introduction

Cost-of-illness (COI) studies are a type of economic study common in specialist clinical journals. The aim of a COI study is to identify, measure and value the economic burden of a disease and estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated.(1, 2) All these impacts are conventionally referred to as 'costs' and translated into monetary values where possible, the universal language of decision makers.(3) Estimates of the COI are useful to inform decisions about service provision and resource allocation in policy agenda setting.(4, 5) These tell us how much society is spending on a particular disease as well as the contribution of different cost components.(6) As demonstrated by Luengo-Fernandez and colleagues, COI studies can enable comparisons between the burden of different diseases (stroke, overall cardiovascular disease, overall and specific cancer) and across years when using the same methodology.(2, 7-10) Comparisons of costs across disease areas are useful to aid decision makers to prioritise scarce healthcare resources to areas with the highest burden.(11)

However, COI studies have been subject to a range of criticism. Firstly, one can be distracted from the benefits produced from the resources devoted to healthcare by only focusing on costs.(12) Simply identifying an area of high cost does not provide enough information to suggest an inefficienct resource allocation. Secondly, it focuses on a single illness without acknowledging that resources saved if the illness is prevented or eradicated will likely be balanced by increased spending on treating another illness.(12) Despite the ongoing debates on their usefulness,(6, 13) COI studies have become a common analytical and public advocacy tool, and they are conducted on a widening range of health conditions and risk factors,(14) such as comorbidities. Indeed, it is important to understand not only the health gains, but also where costs are being incurred and what cost savings are

occurring as a consequence, when making health policy decisions in the face of ageing populations, rising healthcare expenditure and evolving treatment pathways.

The information provided by COI studies is useful to develop preventive efforts which may reduce the burden of disease, particularly for chronic diseases that impact heavily on health expenditures and productivity loss for the whole society.(15, 16) As stated by the Economic Cooperation and Development (OECD), "Chronic diseases … have important labour market impacts for people living with these conditions: reduced employment, earlier retirement, and lower income."(17) It is essential for policymakers to know where costs are incurred. Consequently, appropriate interventions can be implemented and prioritised, such as investing in prevention and early detection of chronic diseases or developing adequate policy frameworks and incentives to support the (re)employment and retention of salaried employees.(18) Over the past two decades, interest in long-term conditions (LTCs) and MLTCs (multiple LTCs) has been growing rapidly.(19-23) Traditionally, coexisting LTC or comorbidity has been defined as the “existence or occurrence of any additional entity during the clinical course of a patient who has the index disease under study”.(24) The accumulation of LTCs within an individual is associated with worse outcomes than having no other chronic conditions or a single condition.(25) MLTCs has been confirmed as the best predictor of sustained high costs; often, the coexisting conditions may incur higher costs than the actual index disease.(26-30) Therefore, MLTCs is now an established priority for both research (31) and clinical practice (32, 33) owing to the high prevalence of coexisting diseases among patients, particularly with ageing populations.

A COI study consists of measuring and valuing resources related to an illness, under which resources consumed are measured and ascribed using a monetary value.(2) As explicitly stated in Jefferson et al. (2000), "the aim of COI studies is descriptive: to itemise, value,

and sum the costs of a particular problem with the aim of giving an idea of its economic burden."(34) Hence, when conducting COI studies, it is required to identify, measure and value the costs that a disease and its comorbidities can generate.(34) Typically, COI studies stratify costs into direct and indirect costs: the former includes costs directly related to the illness, while the latter represents costs due to lost or reduced productivity caused by the illness. However, inconsistencies in the designs and methodologies that are used in COI studies,(35-37) and a lack of transparency in reporting have made interpretation and comparison between jurisdictions/settings difficult and limit their usefulness in healthcare decision making.(14, 38) Variations include data sources, perspectives, cost components, and costing approaches.[7] On the other hand, while standardisation of methodology through the implementation of guidelines is becoming increasingly important, some flexibility may be required for diseases with unique characteristics to be adequately described.(15, 39) Therefore, presenting the methodology and context in considerable detail is vital for users to assess the accuracy and reliability of the cost estimates.

Rheumatoid arthritis (RA), as one of the most common chronic diseases, is a leading cause of work disability worldwide.(40-44) The consequences for morbidity are more important than the effect on mortality.(45) Although numerous COI studies have attempted to quantify the economic burden of RA, the cost estimates vary substantially due to different methodological approaches, perspectives and settings. For example, the global comprehensive approach and medicalised approach are two different methods that measure all costs incurred by patients with the RA and the costs directly attributable to RA, respectively.(46) Although differences in terms of the methods used to calculate costs serve different purposes, this can lead to significant variations in cost estimates within the same disease. On the other hand, a literature review concluded that indirect costs can vary from less than 20% to as much as 50% higher than direct costs across studies, which can largely be explained by the different methodological approaches used, such as the human

capital and friction cost approach.(47) Notably, as RA is a disease predominantly affecting women, failing to include or measure the impact on indirect costs properly will lead to unequal representation of costs incurred by men and women,(48-52) and significantly underestimate the true COI.

As elaborated above, there are deficiencies in COI studies of RA even in high-income countries (HIC). These difficulties are, however, being magnified in low- and middle-income countries (LMICs). As noted by Briggs,(53) there are often differences in methodology adopted by researchers working in LMIC settings as compared to those working in HIC settings, resulting from different contexts. Several anticipated differences in cost components and associated challenges need to be considered when conducting a COI study in LMICs: the main challenge concerns limited and poor-quality resource utilisation data, which are vital requirements for measuring the identified cost items.(54-59) In the LMIC setting, it is less likely to have a robust database for health records. For indirect costs, a widely recognised challenge is that informal employment is common, and income is often seasonal in LMICs.(60, 61) Therefore, it is still uncertain whether the approaches to valuing indirect costs which were developed for a HIC setting are also relevant to an LMIC setting where the labour market operates quite differently.

To explore the differences in estimating COI, two case studies were developed in diverse contexts: Scotland and Tanzania. Both studies were complementary to each other in terms of different approaches and contexts to estimating COI. The former was in a high-income country with novel treatments, well-established knowledge of RA, and an accessible healthcare environment with comprehensive health insurance coverage. Secondary data analysis from a RA inception cohort linked to routinely collected health records was employed to estimate the COI. Furthermore, the impact of coexisting LTCs on people with early RA was investigated. In contrast, the latter was in an LMIC setting with limited

treatment options, little policy intervention on RA, relatively inaccessible healthcare, and heavy reliance on financial costs borne by households. Furthermore, in the absence of routinely collected health data and the availability of screening tools for RA as it requires a blood test, a widening criterion of musculoskeletal (MSK) disorders was adopted. A context-specific questionnaire was developed to collect primary data to estimate the COI of MSK in Tanzania.

1.2 Objectives

This thesis set out to improve the estimation of COI, specifically for two case studies of RA in Scotland and MSK disorders in Tanzania. This introductory chapter identifies the evidence gap in the literature. To answer the overarching aim, this thesis is split into three main empirical parts. Firstly, a systematic review of contemporary COI studies in RA was conducted to map the existing evidence on COI of RA. In particular, this systematic review examined how costs have been measured, estimated, assembled and interpreted based on available data. Secondly, two case studies were performed in diverse contexts: Scotland and Tanzania. As introduced in Section 1.1, both studies were complementary to each other in terms of different approaches and contexts to estimating COI. Lastly, recommendations were produced for improving the estimation of COI studies based on findings from the case studies. Four research questions for the work are presented as below. This is followed by a description of the thesis structure.

1) How has the COI in RA been estimated in the current literature?
    - What are the methodological approaches to estimating the COI in RA?
2) What is the COI of RA in Scotland?
    - How do coexisting long-term conditions impact on the COI in people with early RA?

- What are the methodological challenges in estimating the COI in RA using an inception cohort linked to routinely collected health data?

3) What is the COI in people with musculoskeletal disorders in Tanzania?
   - What are the methodological challenges in estimating the COI in low- and middle-income countries?
4) How could the estimation of COI studies in RA/MSK be improved?

1.3 Structure of Thesis

Following the introduction and objectives for this thesis, this chapter concludes with an overview of this thesis. This overview is visualised in Figure 1.1.

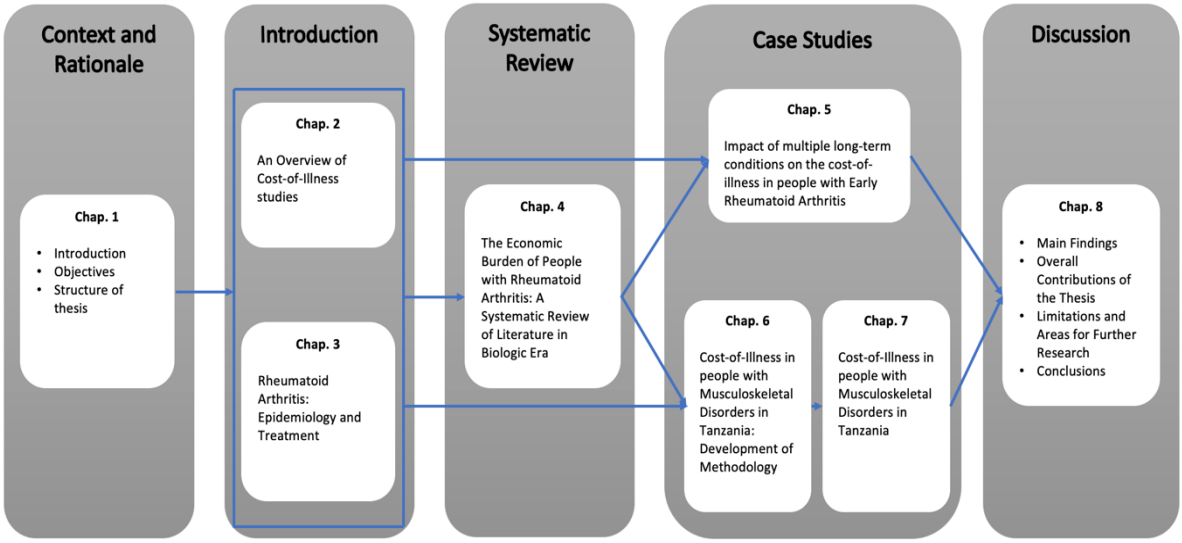


Figure 1.1 Visualisation of the thesis structure

Chapter 2 describes and critiques the essential theories and developments in COI studies. These include the role of COI studies, identification, measurement, valuation of costs and a critical description of COI studies focusing on the reliability and comparability of cost estimates across studies.

Chapter 3 provides a short background of RA, including the epidemiology, symptoms, prognosis and management. Since the introduction of disease-modifying antirheumatic drugs (DMARDs) in the late 1990s, it has offered potent options for patients with inadequate response to conventional synthetic DMARDs. However, these targeted therapies are significantly more expensive than the previous conventional DMARDs.

Chapter 4 presents a systematic review (now published) of COI studies in RA (62) in the biologic era, composing a foundation for the two cases studies under different scenarios. The systematic review identifies how the COI has evolved in people with RA and how it has been measured in the existing literature. In addition, this chapter offers a synthesis of results across studies with high heterogeneity. Given healthcare and related costs vary across different countries and healthcare systems. A single estimate of global COI would not be meaningful or applicable across different settings. This systematic review has focused on the similarities and differences across these studies and how these impact the overall COI. Moreover, the Synthesis Without Meta-analysis (SWiM) checklist [12] was adopted to ensure the robustness of the synthesis approach in this review. The findings suggest that drug costs comprised the main cost component of direct costs in the biologic era while the proportion of hospitalisation was decreasing over time. Economic analyses without taking indirect costs into account or measuring properly will underestimate the full economic impact of RA.

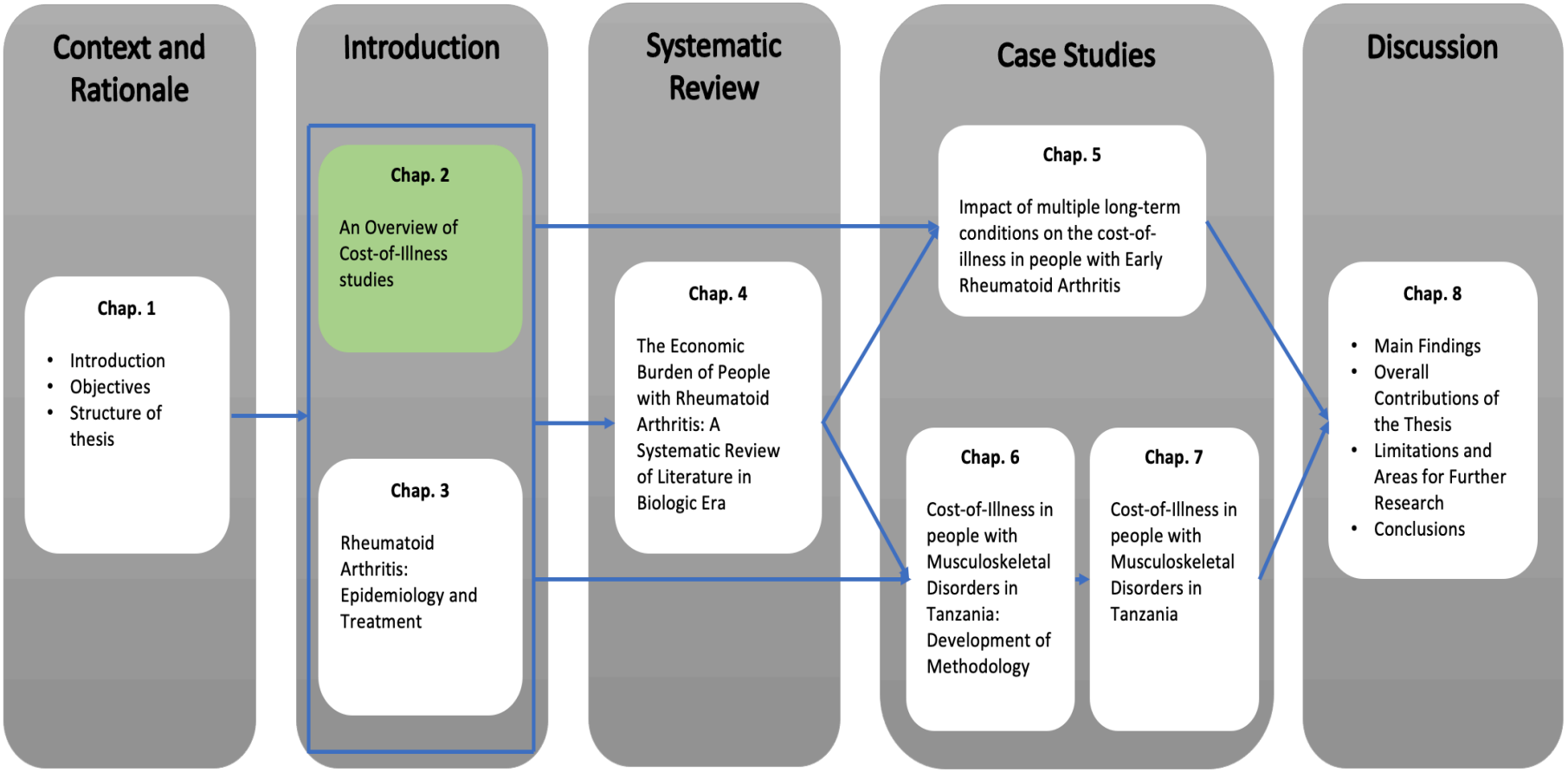
Chapter 5 presents the case study estimating the COI in people with newly presented RA by analysing data from a RA inception cohort linked to routinely collected health data in Scotland. This COI study was developed by leveraging the benefits of linking national cohort and administrative data together and discussing the methodological challenges. In addition, it investigates the impact of coexisting LTCs on the COI in RA by using the most comprehensively used comorbidity measure, Charlson Comorbidity Index, to categorise

distinct LTC burden. While specific LTCs in established RA are known to incur additional healthcare costs, little is known about the impact of multiple LTCs on the COI in early RA, particularly for indirect costs. The findings provide additional support for the importance of active screening of multiple LTCs in people with RA. Both RA and LTCs-related outcomes should be considered in formulating evidence-based policies and guidelines for RA management.

Chapter 6 and Chapter 7 present the methods and results of the LMIC COI case study, which was developed from a broader societal perspective in an LMIC setting, focusing specifically on the case of MSK disorders in Tanzania. Although Chapter 2 has discussed the theoretical background of COI studies and the conventional methodologies, however, several anticipated differences in cost components and associated challenges need to be considered when conducting a COI study in LMICs. Chapter 6 presents and discusses different methodological challenges when conducting COI studies in LMICs. The case studies in LMICs from the systematic review for COI studies in Chapter 4 were used to inform critiques of existing COI studies in LMICs. Finally, this chapter presents the development of a context-specific questionnaire, addressing the outlined methodological challenges.

Following the development of the methodology in Chapter 6, Chapter 7 estimates the empirical COI in people with MSK disorders by using the context-specific COI questionnaire. In addition, as LMICs usually do not offer comprehensive healthcare coverage, financial costs are largely borne by households. Other financial barriers, such as inaccessible health care and transportation, may also prevent people from seeking care. Therefore, scenario analyses were conducted to explore the uncertainty around the health-seeking behaviour and household out-of-pocket expenditures on health to understand the impact from a societal perspective.

Finally, Chapter 8 summarises the main findings of the thesis, limitations inherent in the methods, its contributions to policy implications, and areas where further research is necessary.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CHAPTER 2. AN OVERVIEW OF COST-OF-ILLNESS STUDIES

2.1 Introduction

This chapter aims to describe and critique the essential theories and developments in COI studies. As outlined in Chapter 1, COI studies measure the economic burden of a disease and estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated.(1) This chapter begins by introducing COI studies, identification of cost components, measurement and valuation of direct and indirect costs. A comprehensive overview is provided regarding different COI methodological approaches that have been developed, as well as their strengths and limitations. Furthermore, methodological challenges in terms of reliability and comparability of COI estimates and ongoing debates on the relevance and usefulness of COI studies in healthcare resource allocation are discussed.

2.2 Cost-of-Illness Study

COI studies are a type of economic study common in the medical literature. The aim of a COI study is to identify, measure and value all the cost domains of a particular disease, including direct, indirect and intangible costs.(63) As explicitly stated in Jefferson et al. (2000), "the aim of COI studies is descriptive: to itemise, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden."(34) All these impacts are conventionally referred to as 'cost' and translated into monetary values where possible.(3) The term 'cost' in health economics refers to the value of the consequences of using a particular good or service.(64) That value corresponds to the best alternative use of those resources, the so-called 'opportunity cost'.(64) The information on the economic impact of diseases at a population level is instrumental in public health policy-making,(16) including defining the magnitude of the illness in monetary terms, justifying intervention programmes, assisting in the allocation of research funds, and providing an economic

framework for programme evaluation.(15) Estimates of the COI can inform us how much society is spending on a particular disease and the contribution of relevant cost components.(6) Indeed, COI studies have been used by the World Bank and the World Health Organisation in the past three decades.(65-67) Moreover, COI studies can enable comparisons between the burden of different diseases and across the year when using the same methodology.(2, 7-10) Comparisons of costs across disease areas are useful to aid decision-makers in prioritising scarce healthcare resources for areas with the highest burden.(11)

Since Dorothy Rice formalised the methodology for costing illness in the mid-1960s, (63) several guidelines for conducting and reporting COI studies have been published in the health policy and health economics literature.(14, 16, 39, 46, 68) The number of COI studies has also been escalating with time: Hodgson and Meiners (1982), in their guide to common COI methodological practices of the time, estimated there were around 200 COI studies published between 1960 and 1980.(69) In the decade 1995-2005, Akobundu et al. estimated nearly three times that number, with a trend away from comparing aggregate disease categories in the early works to, later, more of a focus on narrowly defined illnesses.(46) The trends are potentially due to both better data and methods as well as public interest in high-profile conditions (e.g. diabetes) and growing non-public funding of COI studies.(16)

However, there are limitations to the use of COI studies. Although COI studies can demonstrate which diseases may require increased allocation of prevention or treatment resources, they are limited in determining how resources are to be allocated as they do not measure benefits compared to cost-effectiveness analysis or cost-utility analysis.(1, 38) In addition, COI studies focus on one illness without acknowledging that resources saved if

the illness is prevented or eradicated will likely be balanced by increased spending on treating another illness, which is the partial equilibrium approach in economics.(12) Despite the ongoing debates on the usefulness in health decision making,(6, 13) COI studies have attracted much interest from public health advocates and healthcare policy makers.(14)

Nevertheless, studies can vary by perspective, data sources, costing methodologies, and particularly in relation to which cost elements are included, and costing methodologies, lead to widely varying results from COI studies.(69) This is the key reason why the findings of COI studies have been questioned as being difficult to interpret or compare across studies, with many authors identified through the literature review noting the problems with reliability and comparability of estimates.(14, 46) For example, Luppa et al. found depression case costs varied ten-fold for 'direct' costs and 60-fold for 'indirect' costs.(70) Ehteshami-Afshar et al. found a 20-fold difference in direct costs of in their global analysis of recent COI studies in asthma.(71) Salmon et al. found cost differences ranged up to 65-fold in their review of COI in osteoarthritis.(72)

2.3 Identification of Cost Components

Traditionally, cost components can be divided into three categories: direct, indirect, and intangible costs. Intangible costs were found in the literature to be more uncertain in scope or more difficult to price,(70, 73, 74) with variation depending on the estimation method used.(75) Intangible costs incorporate pain and suffering, anxiety or fatigue due to an illness, which can include environmental or intergenerational impacts or loss of wellbeing.(74, 76, 77) There is considerable uncertainty surrounding intangible costs and in addition some authors were reluctant to place a value on human life.(64, 78) For these reasons, intangible costs have frequently been omitted from COI studies historically. When

included, some authors (14) conclude they are best expressed in non-monetary terms. However, others recommend monetising intangibale costs (79, 80) so that they can be measured and valued through “the utility or willingness-to-pay (WTP) approach.(5) Given intangible costs are not commonly included in COI studies and controversies around monitising these costs, (39, 81) this thesis will focus on direct and indirect costs only.

2.3.1 Direct Costs: Medical and Non-Medical Costs

Direct costs measure the opportunity cost of resources used for treating a particular illness.(1) Being incurred by the health system, society, family and individual patients, direct costs consist of medical and non-medical costs. The former includes healthcare expenditure for medication, hospitalisation, outpatient attendance, diagnostic examination, rehabilitation, etc., while the latter is related to other resources such as transportation to the healthcare provider, costs of home or car adaptation, and informal care. Examples of common cost items are presented in Table 2.1.(82)

Table 2.1 Examples of cost components measured in cost-of-illness studies

Direct costs		Indirect costs
Medical costs	**Non-medical costs**	
Diagnostics	Transportation	Paid work
Imaging	Meals	Absenteeism
Laboratory test	Home or car adaptation	Presenteeism
Medications	Informal care	Unpaid work
Prescription		Household work
Non-prescription		Care work
Hospitalisation		Volunteer work
Outpatient attendance		Foregone Leisure time
Emergency room visit		
Medical devices		
Rehabilitation		
Physician services		
General practitioner		
Specialist		
Treatment services		
Surgery		
Consumable suppliers		
Radiation therapy		
Blood products		
Special diets		

Adapted from Jo et al.(82)

2.3.2 Indirect costs: paid and unpaid work

Indirect costs refer to the value of resources lost due to morbidity and mortality, borne by the individual, family, society, or the employer.(82) In paid work, costs due to lost or reduced productivity caused by the disease include work absence (termed ‘absenteeism’) and decreased productivity for those who continue to work (termed ‘presenteeism’).(83) The exclusion of indirect costs will lead to underestimating the total COI, particularly for chronic conditions causing work disability. The frequent exclusion of indirect costs in COI may be due to the lack of guidance and standardisation of methodology. This is also primarily driven by data availability, which varies among countries.(84-86)

Paid work

Two types of productivity loss related to paid work are identified: absenteeism and presenteeism. Absenteeism refers to productivity loss related to not attending work due to illness. Such losses occur if people are too sick to work or visit the healthcare provider during working hours. In contrast, presenteeism relates to reduced productivity at work due to health problems.(87, 88) If a person suffers from illness but does attend work, the quality and quantity of work performed may be lower compared with the quality and quantity of work performed when in full health.(89)

The significance of presenteeism for the value of indirect costs has been highlighted in existing literature.(90-92) Costs associated with presenteeism can be substantial, in some cases even outweighing those related to absenteeism.(93) Still, despite the high costs associated with presenteeism in these cases, it is seldom included. For example, a recent systematic review for COI studies for low back pain shows costs for presenteeism can account for 70% and 80% of indirect costs;(94, 95) however, it is often underexplored.(83) Consequently, indirect costs based on absenteeism alone will only partly reflect total societal indirect costs.(96, 97) A sound methodological framework for the assessment of presenteeism poses a challenge, but the potential impact of presenteeism on costs needs to be included in order to improve the reliability of results.(91, 92)

Unpaid work

Unpaid work is the production of goods and services that are not sold on a conventional market.(88) Commonly, three main types of activities can be distinguished, including household work, care work, and volunteer work.(98) Although unpaid work is a non-market good, it is of great economic value and contributes significantly to societies' welfare, particularly for the diseases that are prevalent in certain demographic groups (such

as females, children and elders). Globally, women undertake three times more care and domestic work than men, with women in low- and middle- income countries (LMICs) devoting more time to unpaid work than women in high-income countries.(99) Therefore, if unpaid work is not collected in addition to paid work, COI estimates will be biased against women, particularly for the disease predominantly affecting women, like RA.

2.3.3 Perspectives

COIs may be carried out from various perspectives, providing helpful information on the economic burden to the particular group. Perspectives should refer to who bear the costs, which can be from the whole society, payer, patient, or employer. Onukwugha et al. found the societal perspective accounted for 46% of COIs between 2005 and 2014, followed by the patient's perspective (10%); however, 26% of COIs not stating the study perspective.(100) The adopted perspective is closely linked to the study purpose and includes slightly different cost components that eventually lead to a diverse and wide range of results for the same illness.(46, 101) The cost components in each perspective are provided in Table 2.2.

Table 2.2 Costs included in COI studies by perspectives source

Perspective	Direct costs		Indirect costs
	Medical cost	Non-medical cost	
Societal	All costs*	All costs*	All costs*
Payer	Covered costs	Covered costs	
Patient	Out-of-pocket costs	Transportation/ Informal care	Wage loss
Employer			Absenteeism / Presenteeism

* This refers to all costs attributable to an illness, subject to data availability of each study. Source: Luce et al.(102)

Societal perspective

The societal perspective is the most comprehensive and generally preferred by economists.(4, 5, 14, 103) This perspective includes all cost items in direct and indirect costs, which allows an analysis of all relevant opportunity costs attributable to an illness.(82) This is particularly essential when designing healthcare policies as it needs to address multidimensional benefits and costs. When conducting a COI study from a societal perspective, it may take a 'pragmatic' approach to valuing the opportunity cost of healthcare resources,(69, 104) using market prices as proxies for the monetary value of foregone alternative uses of resources.(5)

Payer's and Employer's perspective

While the societal perspective includes all cost components, a payer's perspective mainly focuses on covered costs, particularly medical costs from a healthcare system. The covered costs include resource use such as diagnostics, drug treatment, monitoring, outpatient attendance, hospitalisation, and other healthcare expenditures. Although a societal perspective is usually favoured, it is not feasible in some instances, such as rare diseases with limited data. In this case, data from a payer's perspective may be more reliable and available.(1)

In contrast, an employer's perspective focuses on productivity loss from paid work, including both, absenteeism and presenteeism.(105) In this case, productivity losses related to unpaid work do not need to be included. In addition, other costs such as worker's compensation insurance premiums and worker replacement costs (recruitment, training, retraining) are often taken into account.(14, 106)

Patients' perspective

As shown in Table 2.2, out-of-pocket expenditures are important to be incorporated in COI studies from the patients' perspective, including personal/household payments on health, travel cost to attend medical appointments, informal care, adaptation to make a house or car more accessible for patients, and other costs such as meals eaten outside when receiving health care. However, many of these expenses are usually excluded due to the difficulty of measurement and valuation when considering the economic burden of a disease. Still, they can constitute an important source of related costs,(64) particularly in the context with limited health insurance coverage, such as LMICs.

Moreover, informal care has been rarely included until recently.(107) There is a growing interest in including informal care as part of non-medical costs,(108-115) although it is not straightforward to define due to its heterogeneity.(116) The COI could be underestimated without taking informal care into account, especially for diseases that cause significant limitations on functional disability.(117) Importantly, when care is provided by non-professional people, generally by family members, close relatives, friends or neighbours, it may be free of charge to public administrations. Still, it has its own 'hidden costs': the spillover effect to carers, such as productivity loss, detrimental health, and psychological effects.(118-121)

2.4 Measurement and Valuation of Cost-of-illness

2.4.1 Prevalence and Incidence-based Approaches

Fundamentally, there are two approaches to estimating COI: prevalence and incidence-based approaches. The prevalence-based approach estimates the total cost of a disease incurred in a given year, while the incidence-based approach involves calculating the lifetime costs of cases first diagnosed in a particular year, providing a baseline against

which new interventions can be evaluated.(122) The approach adopted depends on the concept and the purpose of the study. If the results are to be used for an insight in the distribution of costs or for cost containment within a limited time span, the prevalence-based approach is appropriate, since this approach identifies the main components of current health expenditure.(37) In general, the prevalence-based approach may be more feasible to measure the COI for chronic conditions whose costs remain relatively stable over time, such as chronic bronchitis.(82, 123) However, it needs to be interpreted as a snapshot of the costs in the given year, rather than the costs that could be saved if all cases of the illness were averted.(1, 15, 38, 69)

In contrast, if the analysis is aimed at making decisions about the choice of treatment or research strategy to implement from the perspective of efficiency, the incidence-based approach is more appropriate because it provides the basis for predictions about the likely savings from programmes that reduce incidence or improve health status.(37) The incidence-based approach can show how costs vary with disease duration, which may be useful for clinical and therapeutic guidelines in planning interventions targeted at specific stage, such as breast cancer.(14, 124-126) However, they can require substantial data (73) and a number of assumptions about the future course of illness.(1, 127) The literature noted that, in a population with static demography and epidemiological risk, prevalence equals incidence multiplied by average duration and, since incidence-based future costs are discounted, prevalence-based costs would be greater than incidence-based costs.(128) The higher the discount rate, the larger the prevalence-based COI estimates compared to estimates obtained using an incidence-based approach.(129)

2.4.2 Measurement and Valuation of Direct Costs

As described in Section 2.3.1, direct costs for health care include any direct expenditures associated with illness, including medical and non-medical costs. Estimation of direct costs involves first estimating quantities of resource use (e.g. the number of outpatient attendance, number and types of drugs, number and types of diagnostics), and second valuing those resources by applying relevant unit costs.

Top-down and bottom-up approaches to estimating cost-of-illness

Measurement of COI studies can be done using either a top-down or bottom-up approach.(35) These data can be obtained from national healthcare statistics, medical records, insurance claim databases, and hospital billing records. The top-down approach, also known as the epidemiological or attributable risk approach, measures the proportion of a disease due to exposure to the disease or the risk factors.(35, 130) It calculates the attributable costs using aggregated data and a population-attributable fraction (PAF), also known as an epidemiological measure.(130-132) An assumption needs to be made that there is no association between two diseases. In addition, relevant confounding factors, such as age, sex and other socioeconomic factors, may need to be controlled for; otherwise, the relative risk and the value of PAF could be biased.(1)

The main advantage of the top-down approach is that it provides the allocation of total healthcare expenditures among the major diagnostic categories in a given country.(38) However, cost components regarding non-medical costs, such as transportation and informal care, are less likely to be included when using a top-down approach. While the top-down approach usually requires more information to calculate the PAFs, multiple data sources for unit costs and utilisation of healthcare resources would be needed for the bottom-up approach.

In the bottom-up approach, the total costs are generated through the multiplication of unit costs by the quantities used. A review of current COI methodologies shows the bottom-up approach was used to derive the cost estimates in most COI studies (83%), while only 11% of studies used the top-down approach.(100)

Global Comprehensive Approach and Medicalised Approach

As outlined in Chapter 1, the global comprehensive approach and medicalised approach are two different methods that estimate all costs incurred by patients with the disease of interest and the costs directly related to the disease of interest, respectively.(46) The global comprehensive approach calculates costs by identifying all patients with a diagnosis of the disease of interest and summing all costs.(100) The strength of the global comprehensive approach is its simplicity, requiring only a diagnosis of the disease, and offers a quick and useful way to estimate the COI in certain diseases. For example, medical costs incurred by patients with AIDS may seem relevant to the disease itself.(1)

In contrast, the medicalised approach identifies all patients with a diagnosis of the disease of interest and sums all costs associated with the diagnosis. The medicalised approach may underestimate the COI if fails to include all relevant costs. For example, the costs for CVDs may not necessarily be included in a COI study for rheumatoid arthritis (RA). However, the costs of CVDs may be indirectly attributable to RA, since clinical evidence has shown that uncontrolled RA can increase the complications of CVDs.(133, 134) As the medicalised approach estimates the COI by restricting its attention to health expenditures related to the diagnosis of the disease of interest. It is not feasible to estimate the impact of coexisting long-term conditions in chronic diseases.

2.4.2 Measurement and Valuation of Indirect Costs

When measuring indirect costs, most COI studies rely on subjective productivity changes by using questionnaires, which could be validated instruments or designed for specific research purposes. Commonly, questionnaires are administered as a part of the individual or household surveys by asking about the productivity retrospectively during a specific period. To adequately calculate indirect costs, a variety of information would be required.(98) Respondents are asked to complete questions regarding their productivity loss related to absenteeism and presenteeism in paid work, impact on unpaid work or daily activities, given their current health status.(97, 135) In order to increase standardisation and comparability across studies, it may be advised to use validated questionnaires.(98) Several review papers highlight a variety of available questionnaires for measuring productivity loss.(136-139) The majority of questionnaires were developed for use in a specific patient population,(135) where the Work Productivity and Activity Impairment (WPAI), (140, 141) Work Limitations Questionnaires (WLQ) (142) and Health and Work Performance Questionnaire (HPQ) (143) are the most frequently used instruments that seem to be suitable across a broader range of health conditions.(135, 144)

Nevertheless, some flexibility may be required as the context and data availability vary. For example, most questionnaires have not been widely tested in LMICs yet. Given the healthcare infrastructure and labour market in LMICs operate quite differently from HICs, it may be more feasible to develop a tailored questionnaire for estimating COI, accounting for heterogeneity in demography, epidemiology, or resource utilisation in different settings. Besides, a few COI studies have measured productivity loss by linking to social security database, as done with Swedish register data (145-147). However, this would be limited to absenteeism.

Human capital approach (HCA) and Friction cost approach (FCA)

Two competing approaches are used to value paid work in indirect costs: the human capital approach (HCA) and friction cost approach (FCA). The former is generally taken to reflect lost productivity potential. In contrast, the latter only values the estimated actual production lost when it takes to replace the sick worker, known as the 'friction period'.(148)

Historically, the HCA has been most frequently used to estimate productivity costs.(149) The HCA is based on Grossman's human capital model, which regards participation in health care as an investment in human capital – increasing productive ability and the income of the individual.(150) The theoretical justification is the marginal productivity theory by using total employer compensation per worker as a proxy for individual productivity, according to which employers equate the marginal cost of employee time with the expected marginal contribution to output.(151) So the HCA is designed to estimate the value of human capital as the present value of the future earnings under the assumption that future earnings are used as a proxy for future productivity if the individual had continued to work in full health. However, in many cases, the future earnings do not accurately reflect future production.(149) A significant limitation of the HCA from the viewpoint of economic theory is that it does not consider the costs of developing and maintaining a stock of human capital, such as education and personal consumption.(152, 153) Moreover, in practice, the HCA has been criticised due to a solid and controversial assumption that workers cannot be replaced even if the unemployment rate is significantly high. Consequently, this method would overestimate the value of foregone production.(149) There has also been a good deal of criticism of the HCA's ability to capture the value of non-paid work.(154) Nevertheless, time spent in unpaid work can be valued in the HCA using either the individual’s own or imputed wage or the average wage

paid to workers performing similar services (detailed in the later section for valuing unpaid work).(153)

As an alternative in addressing the limitations of the HCA, the FCA was proposed in the mid-1990s, intending as more of a decision-makers approach to evaluation rather than staying strictly in line with welfarist economic theory.(148) The FCA estimates the value of human capital when another person from the unemployment pool replaces the present value of a worker's future earnings until the sick or impaired worker returns or is replaced. Hence, the friction cost is limited to the illness during the friction period. However, it has been criticised that the FCA implies an unrealistic scenario in which unemployment could be solved if employed workers' number of hours worked was reduced. It is argued that, theoretically, if replacement is from within the organisation or from another organisation, with the resulting vacancy being filled in the same way, then there will be a 'replacement chain' with a position ultimately being served by an unemployed person. Correspondingly, there will be no income or productivity loss from a societal point of view in the long run.(149, 155) In addition, the FCA has been criticised for its lack of underlying theory and the fact that it does not value leisure time, resulting in a vast underestimation of the value of lost time or productivity.(148, 156, 157) As introduced in Section 2.2.3, the friction cost approach can be appropriate from the employer perspective but are less likely to be appropriate from the societal perspective.

While the HCA may overestimate actual production losses, the FCA is relatively difficult to implement. It requires detailed information or assumptions about labour market conditions and behaviours and the technical knowledge to translate these into realistic friction periods.(129) As a result, the friction period varies across studies; the period ranges from 6 weeks to 6 months in the existing literature.(153) According to a systematic

review for COI studies using FCA from 1995 to 2017, 51 out of the 80 included studies came from Canada, Germany, and the Netherlands, the three countries which had officially endorsed the FCA.(153, 158) However, the justification for the choice of one method over the other is not clear and there is ongoing debate as to the best method.(87, 148, 159) A review and assessment of the evidence suggests that a pragmatic approach is to use both the HCA and FCA approaches as sensitivity analyses.(160)

US panel approach

The US Panel approach values indirect costs not in monetary terms but in terms of quality-of-life (QOL) effects related to income changes due to health.(4) The theory is QALYs take account of the impact on income (and hence general wellbeing) for the individual providing health state values. This impact lasts for as long as the individual is away from work. Associated consumption and costs to the employer in the friction period should be valued in monetary terms.(4) However, the reliability of this approach has been debated and has also been extensively tested empirically.(161-169) The results indicate that QOL measures do not adequately capture the impact of ill-health and treatment on productivity and income. For example, whether and to what extent respondents have incorporated the impact of changes in income into the valuations used to scale these instruments is unclear. Also, individuals may be protected from a loss of income while sick by the social or private insurance coverage. Applying the US Panel approach to quantify productivity loss is therefore not recommended.(98)

In the second US panel approach,(170) it is acknowledged that evidence is not definitive that the effects of morbidity on leisure are necessarily reflected in the utility scores or QOL weights. In addition, productivity and the effects of morbidity on leisure activities captured

in preference-based measures could lead to double counting. Research recommendations are made to develop improved QOL weights to avoid such double counting.(170)

Measurement and Valuation of Presenteeism

Although not as straightforward as absenteeism, several approaches to measuring presenteeism have been developed in various instruments, including the perceived change approach, comparative productivity approach, and unproductive time while at work (direct approach).(91, 140, 142, 143, 171, 172) However, concerns about the methodology of measuring presenteeism are not uncommon in the literature. For example, it has been argued that the inclusion of a benchmark level of productivity provides more meaningful results than perceived impairment alone;(143, 171) employees cannot accurately estimate unproductive time in practice, thus limiting its usefulness.(91, 171, 172) Several fundamental questions include the comparability between instruments, validation against an object measure, generalisability across a wider variety of employee groups, and the extrapolation of estimates to a yearly prevalence based on an optimal recall period.(137, 138, 173-177)

Following the concerns over measuring presenteeism, the uncertainty about the measurement step shapes any discussion about valuation, although valuation has its challenges. Over the past few years, several competing methods have been proposed to monetise productivity loss due to presenteeism:

Human Capital Approach and Friction Cost Approach

Similar to measuring absenteeism, the HCA and FCA have also been adapted to monetise presenteeism.(136) Presenteeism hours obtained from the valuation stage are used in place of the sickness absence days to obtain the monetary loss due to presenteeism. Often the

HCA is preferred due to its computational convenience and consistency with contemporary economic theory.(138)

Team Production Method (TPM)

The TPM is based on multipliers that take into account factors such as the replaceability of an employee, the contribution of an employee as part of a team, and the time-sensitivity of an employee's work.(178, 179) Nevertheless, the practical challenge is that an extensive library of multipliers must be developed, maintained, and updated. Moreover, the generalisability to other organisations of the same type may be limited as TPM is based on individual-level characteristics and managers' perceptions.(135)

Firm or Introspective Method (FIM)

The FIM method is based on a manager's information about the company's cost in using countermeasures against productivity loss.(138, 179) The FIM believes that the worker does not fully understand the magnitude of the lost productivity due to presenteeism. In contrast, it is assumed that managers have a good sense of how their company's productivity is affected by health-related problems and rely on their perception.(135) However, many cost factors could be intangible and difficult to conceptualise. The validity remains untested and has not yet been benchmarked against the HCA/FCA approach.(180)

Valuing Unpaid work

As mentioned in Section 2.3.2, unpaid work is the production of goods and services that are not sold on a conventional market.(88) Commonly, costs for unpaid work can be derived through two approaches: proxy good approach and opportunity cost approach.(5, 181-183) The proxy good approach values the unpaid labour at the market price that would need to be paid to find a replacement from the labour market to do the work. For example,

housework can be valued using the average price of a professional housekeeper. In contrast, the opportunity cost approach is based on a person's net wage in paid work. For people who are unemployed, potential wages (previously paid job or minimum wages) would be used. However, as there is no clear consensus, it may be recommendable to choose one approach to value unpaid work, and consider the other as an alternative in the sensitivity analysis.(5, 98, 102) Similar to the valuation of paid work, the value of unpaid work should represent the actual population in practice. Therefore, it may be appropriate to base values on the average age- and sex-specific wages.(98)

2.5 Estimating/Analysing Costs Approaches

The econometric approach estimates the incremental costs between a cohort with the disease and another cohort without the disease. The matched control and regression approach are two major methods, providing various mechanisms for isolating the costs specifically due to the disease.(1)

Matched control approach

The matched controlled approach is to identify all patients with a diagnosis, then sum cost and subtract out the average cost of a matched cohort to find incremental costs.(46, 100) One of the assumptions of the matched controlled approach is that there is no need to adjust for confounding factors once the matching algorithm has been applied.(46) Ideally, only the systematic difference of COI estimates between the groups would be obtained when the matching is applied correctly. Unfortunately, due to unobservable differences, this degree of matching is nearly impossible by using administrative claims databases to estimate COI in many common studies.(46)

Regression-based techniques

The regression approach derives the COI estimate from the estimated coefficient on an indicator variable for diagnosing the disease in the regression model.(46) In COI studies, the regression analysis is commonly used in the literature to consider two important characteristics of the distribution of health care expenditure: the large number of subjects with zero expenditure and the heavily skewed distribution.(106, 184-189) The ordinary least square (OLS), generalised linear model (GLM) and two-part model (TPM) are different types of regression models routinely used in the analysis of costs within a healthcare context to explain variation in costs, which are briefly introduced in the following:

- *Ordinary Least Square (OLS) and log-transformed OLS*

The OLS regression is one of the most popular models used for continuous outcomes under the normal distribution assumption.(190) OLS has shown to be a robust method, especially with large data sets.(191) The three components of OLS are a random component for the response variable, which is assumed to be normally distributed; a systematic component representing the fixed values of the explanatory variables in terms of a linear function; lastly, a link function that maps the systematic component onto the random component.(190) When used for COI study, assumptions of standard OLS regression are unlikely to be met given cost data are often skewed. Costs are usually non-normal and heteroscedastic, and relationships may not be truly linear. Violation of OLS assumptions may mean that normality and efficiency of estimators are not achieved, so not providing the best estimates of the average effects in the population.(192)

Although transformation is used to improve linearity and minimise the issues related to heteroscedasticity and skewness of the data, the transformation has some limitations: 1) the

response variable has back-transformation problems; 2) the transformation must simultaneously improve the linearity and homogeneity of variance, and 3) the transformation does not overcome the protocol of point probability mass at the zero value.(191) For example, log-transformed data provide an analysis of geometric mean costs (193) unless sophisticated back-transformation methods are adopted.(194)

- *Generalised Linear Model (GLM) using gamma distribution with log-link function*

GLMs have a variety of forms characterised by two features: a distribution function for the outcome data (i.e. costs) and a link function that describes the scale on which covariates in the model are related to the outcome.(195) It would be more appropriate for cost data to employ a skewed distribution function, such as a gamma or inverse gaussian distribution.(196) Changing the distribution function but still using the identity link, leaves the interpretation of the coefficients unchanged from the OLS model. Therefore, changing the link function of the GLM alters how covariates are assumed to act on the outcome and thus alters the interpretation of the coefficients.(192) The alternative approaches of modelling healthcare costs have been frequently discussed based on previous literature.(197-201) The most recommended approach is fitting a GLM using a gamma distribution with log-link function,(195) which was found to be a good performance predictor for cost distribution.(198, 201)

- *Two-Part Model (TPM)*

Apart from the heavily skewed distribution in cost data, the other characteristic is the large number of zero expenditures. Various models reported in the literature comprise TPM designed to take zero expenditures into account and has been widely used in health economics and health services research.(202) In the first part of the two-part model, a binary choice model is fit for the probability of observing a positive-versus-zero outcome.

Therefore, the first part models the individual's decision to access health care services, i.e., the probability of having health care expenditure different from zero. Then, the second part models those conditional on a positive outcome with an appropriate regression model. It determines the level of health care consumption in the subsample of individuals with health care expenditure different from zero.(189)

2.6 Critiques and Challenges in COI Studies

As described in Section 2.2, COI studies have become a common analytical and public advocacy tool that can be used to understand the importance of health problems by describing their impact on direct and indirect costs from different perspectives.[10-18] However, COI studies have been subject to many critiques, particularly on their usefulness to healthcare decision making.(6, 154, 203-206) The primary argument is that COI studies do not provide enough information to suggest resource allocation without understanding the benefits gained. Secondly, few diseases can be eradicated so that the marginal cost savings will be less than that indicated by COI studies.

Apart from the ongoing debate on the relevance to healthcare decision making, the reliability of COI estimate and comparability across studies have been questioned.(100, 207-209) Many COI studies have come under scrutiny because variations in COI estimates can frustrate policymakers searching for a definitive answer on the cost of a given illness. Several reviews on the COI studies (208, 209) highlighted the lack of standardisation of methodological approaches, resulting in the wide variation of cost estimates across studies and concluded that the cost estimates across studies should not be compared quantitatively.

Reliability

Questions regarding the reliability of COI estimates arise because of the difficulties in identifying the costs that are specifically due to an illness.(210, 211) As discussed in Section 2.4.2, COI estimates could be biased when attributing costs to the disease that are unrelated to the disease (global comprehensive approach). On the other hand, failing to incorporate all relevant elements (medicalised approach) could not reflect the actual economic burden of the disease. Commonly, many studies use existing data for practical considerations; however, these datasets are not always created for purposes for undertaking COI studies. During the past decades, the evolution of routinely collected electronic data within care services has provided new opportunities for collecting data without burdening patients or caregivers. However, self-reported methods will still be required when a societal perspective is desirable for the intended analysis.(212) Therefore, it will be important that COI studies leverage current trends in health information technology, data availability and data linkage, as well as incorporate patient-centred concerns surrounding the burden of disease (e.g. direct non-medical and indirect costs).(100)

Comparability

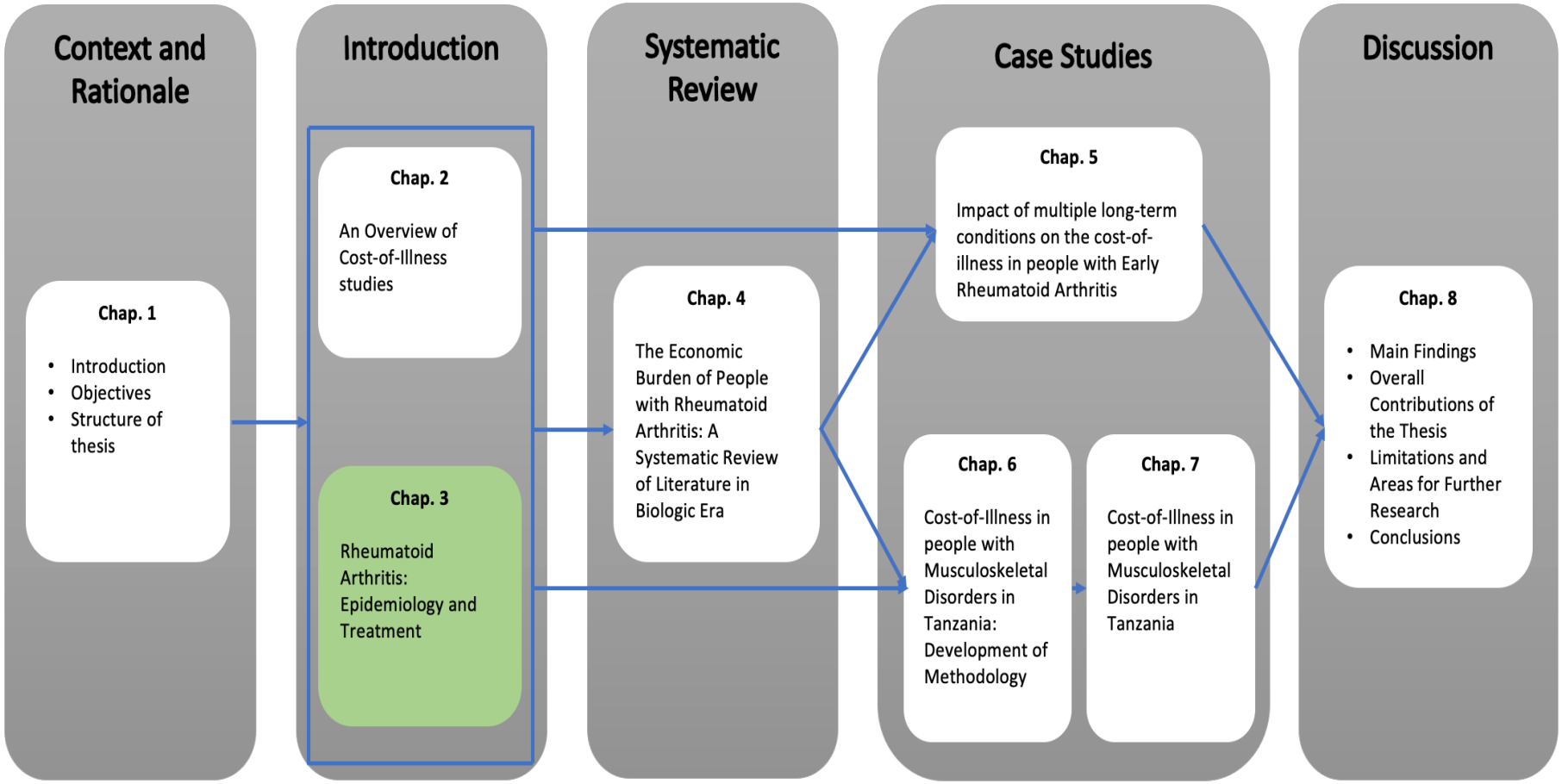
The consistency of COI estimates has been questioned because of documented variations in cost estimates, even within disease areas in a given country. For example, some studies may adjust for comorbidities, disease severity or other patient factors when estimating costs, while others do not. Although the standardisation of methodology and study design for COI studies has been discussed for decades, there is no ‘gold standard’ against which the quality of COI studies could be assessed. On the other hand, some flexibility may be necessary for diseases with unique characteristics to be adequately described.(15, 39) As a result, clear reporting of the study method would be vital to improve cost comparability.(15) These include the cost components, quality of data, possible

confounding factors, the assumptions and approaches to measuring and valuing costs.(14) Moreover, it is crucial to include sensitivity analyses that consider alternative values for all essential parameters and key assumptions.

2.7 Chapter Summary

This chapter provided an overview of key aspects in COI study, including the identification, measurement, valuation of direct and indirect costs, as well as the strengths and limitation in costing approaches and methodological challenges. It shows that there is a need to have clear guidance and standardisation of methodology for COI studies, particular for measuring and valuing indirect costs. The choice of cost methodology can significantly influence the magnitude of estimates, yet it is largely driven by data availability. Moreover, a lack of transparency in reporting have made interpretation difficult and thus limited their reliability and comparability.

In this thesis, COI in rheumatoid arthritis in Scotland and musculoskeletal disorders in Tanzania are used as case studies to improve the estimation of COI studies. The following introductory chapter will describe the epidemiology and treatment in RA as a connection to the empirical works of this thesis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CHAPTER 3. RHEUMATOID ARTHRITIS: EPIDEMIOLOGY AND TREATMENT

3.1 Introduction

As outlined in Chapter 1, chronic diseases have an important impact on productivity for the whole society in addition to incurring substantial healthcare expenditure. Over the past two decades, interest in LTC (long-term condition) and MLTCs (multiple LTCs) has been growing rapidly.(19-23) Traditionally, coexisting LTC or comorbidity has been defined as the "existence or occurrence of any additional entity during the clinical course of a patient who has the index disease under study".(24) In contrast, MLTCs has been defined as the coexistence of two or more LTCs in the same individual.(213) The accumulation of LTCs within an individual is associated with worse outcomes than having no other chronic conditions or a single condition.(25) MLTCs is now an established priority for both research (31) and clinical practice (32, 33) owing to the high prevalence of coexisting diseases among patients, particularly with ageing populations.

Rheumatoid arthritis (RA) is one of the most common chronic diseases. Work disability is a major consequence of RA.(40-44) The consequences for morbidity are more important than the effect on mortality.(45) Coexisting LTCs are frequent and may shorten the lifespan of people with RA,(134, 214, 215) associated with worse health and quality of life outcomes(216-219) and have a significant negative impact on functional ability, independent of disease activity.(220-222) In the context of an ageing population and the life-long nature of RA, MLTCs is particularly relevant in order to provide the best possible outcomes and minimise unintended complications and costs.(23, 223) Dealing with RA not as a single condition, but considering it alongside MLTCs is the current challenge in health research in high-income settings.(221, 223, 224)

This is even more complex for health inequity in low- and middle-income settings (LMIC). Particularly in Africa, fierce competition for scarce resources, difficult access to healthcare providers and the lack of rheumatologists are significant health care challenges.(225) The WHO has recommended that there should be at least one rheumatologist per 100,000 people; however, that is one rheumatologist per 40 million people in sub-Saharan Africa.(226) As a result, when patients seek conventional healthcare, they are often seen at community health centres and receive symptomatic treatment only, such as non-steroidal anti-inflammatory drugs (NSAIDs) or steroids for pain relief.(227)

Due to the shift of focus on improving clinical outcomes in how we approach chronic diseases in medical research, it is pertinent that we also think about how this impacts the way we look at COI. This chapter gives a short background on RA. The following sections will introduce the epidemiology, symptoms, prognosis and management.

3.2 Rheumatoid Arthritis: Epidemiology

3.2.1 Prevalence and Incidence

RA is a chronic autoimmune disease characterised by persistent pain and stiffness, progressive joint destruction, functional disability, and premature mortality.(214, 228, 229) It has been estimated that between 0.5% and 1% of the population are affected worldwide,(230, 231) with a higher prevalence in women than in men.(134) Although the peak incidence is in the sixth decade,(232) it also tends to strike during the most productive years of adulthood, between the ages of 20 and 40 years.(231) From the 1970s to the 2000s, a decrease in the RA incidence has been reported. However, some geographical variations have been observed, although there have also been different methodologies in the epidemiological studies.(230) Incidence in Western countries ranges from 9 to 45 cases per 100,000 per year, with lower incidence observed in South European countries.(233) The American Indians have a higher incidence of RA than other

populations in North America, Europe and Asia.(234, 235) In Africa, although there has been no study found on RA incidence, the prevalence of RA ranging from 0.00 to 0.97% has been reported.(227)

3.2.2 Mechanism and Diagnosis of RA

The pathophysiology of RA involves chronic inflammation of the synovial membrane, which can destroy articular cartilage and juxta-articular bone.(236) The cause of RA is not yet completely understood. However, genome-wide association studies have identified more than a hundred loci associated with RA risk, most of which implicate immune mechanisms.(237, 238) Environmental factors have been linked to the disease as well. Smoking, lower socioeconomic status, periodontal disease, characteristics of the microbiome of the gut, mouth, lungs, and viral infections have been associated with an increased risk of RA.(238-240)

The standard means of defining RA are by use of classification criteria. The classification criteria set that is in widespread international use to define RA are the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria.(241) These criteria are well accepted as providing the benchmark for disease definition. Still, they have a significant limitation in that they were derived by discriminating people with established RA from those with a combination of other definite rheumatological diagnoses. In 2010, a joint working group of the ACR and the European Alliance of Associations for Rheumatology (EULAR) was therefore formed to develop a new approach for the classification of RA (Table 3.1), which has more focus on earlier stages of the disease.(242)

Table 3.1 The 2010 American College of Rheumatology/ European Alliance of Associations for Rheumatology Classification Criteria for RA

	Score
Target population (who should be tested?): patients who:	
1) have at least one joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
One large joint	0
Two to 10 large joints	1
One to three small joints (with or without involvement of large joints)	2
Four to 10 small joints (with or without involvement of large joints)	3
> 10 joints (at least one small joint)	5
B. Serology (at least one test result is needed for classification):	
Negative RF and negative ACPA	0
Low positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3
C. Acute phase reactants (at least one test result is needed for classification):	
Normal CRP and normal ESR	0
Abnormal CRP or normal ESR	1
D. Duration of symptoms	
< six weeks	0
≥ six weeks	1

ACPR: anti-citrullinated protein antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis; RF: rheumatoid factor
Adapted from Aletaha D, et al. 2010 (242)

Criteria for diagnosis include having at least one joint with definite swelling that is not explained by another disease. The likelihood of a RA diagnosis increases with the number of small joints involved (e.g. metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, and wrists). In a patient with inflammatory arthritis, the presence of a rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA), or elevated C-reactive protein level or erythrocyte sedimentation rate suggests a diagnosis of

RA.(242) The new criteria are an effort to diagnose RA earlier in patients who may not meet the 1987 ACR classification criteria. The 2010 criteria do not include the presence of rheumatoid nodules or radiographic erosive changes, both of which are less likely in early RA. Also, symmetric arthritis is not required in the 2010 criteria, allowing for early asymmetric presentation.(242, 243)

3.2.3 Symptoms and Prognosis

RA is a polyarticular symmetric disease that involves multiple joints bilaterally. It usually presents with pain, stiffness and symmetrical swelling of the small joints of the hand and feet. Furthermore, symptoms of fatigue, weight loss and malaise can occur.(230) If RA is insufficiently treated, extra-articular manifestations may develop, such as rheumatoid nodules. A more serious manifestation is rheumatoid vasculitis, a necrotising inflammation of small or medium-sized arteries, mostly involving the skin, vasa nervorum, and occasionally arteries in other organs.(228, 244) In the long run, accumulation of irreversible joint damage will lead to functional disability in patients without sufficient treatment; patients who sustain irreversible joint damage will never recover normal physical function.(245)

The natural history of RA is characterised by a close association between disease activity and progression of joint damage.(246) In practice, disease activity in RA is evaluated by composite measures that include joint counts, i.e., the number of tender and swollen joints. The composite measures are commonly used in trials since they capture the most important disease aspects in a single score. These scores, namely the clinical disease activity index (CDAI),(247) the disease activity score using 28 joint counts (DAS28),(248, 249) or the simplified disease activity index (SDAI),(250) correlate with outcomes such as damage progression and functional impairment.(247, 251) These measures allow quantification of disease activity, and disease activity states based on specific cut-points of these indices

have been defined to help guide treatment. Patients in remission and those with low disease activity can continue regular participation in social and work activities and normal life expectancy.(252)

The Health Assessment Questionnaire - Disability Index (HAQ-DI) (253, 254) is the most widely used measure of function in studies of RA.(255) The HAQ-DI scores range from 0 (no functional impairment) to 3 (most impaired). Worse functional disability is associated with increased cardiovascular events and mortality,(256, 257) joint damage (258) and work disability in people with RA.(259, 260) Functional disability is mainly associated with disease activity in early RA and with radiographic joint damage in people with established RA.(261) Predictors of worse functional disability in the long-term include baseline or 1-year HAQ-DI score,(262-264) older age,(263, 265) female gender,(263, 265) disease activity,(262, 264-266) RF positivity or ACPA positivity,(267) radiographic damage,(258, 264, 268, 269) number of comorbidities,(270-272) and low socio-economic status.(268, 273, 274)

3.3 Rheumatoid Arthritis: Treatment

Therapeutic management of RA consists of the application of disease-modifying antirheumatic drugs (DMARDs). These agents target inflammation and, by definition, also reduce structural damage progression in RA.(238) There are two major classes of DMARDs: synthetic DMARDs and biological DMARDs (bDMARDs). Synthetic DMARDs can be further divided into conventional synthetic and targeted synthetic DMARDs.(238) Conventional synthetic DMARDs are the oldest class of agents, examples of which are methotrexate, sulfasalazine and hydroxychloroquine. The use of these agents has evolved empirically, but their modes of action are still largely unknown.(238) On the other hand, bDMARDs and targeted synthetic DMARDs have been developed to modulate specific targets in the inflammation process.(238) A new type of medicine, JAK inhibitors,

offered people who cannot take DMARDs, or bDMARDs, or tried them but found they are not effective.(275) Other treatment options include pain relief by steroid or NSAIDs, surgery, and supportive treatments, such as physiotherapy and occupational therapy.(275)

The EULAR and ACR publish and update their guidelines for RA treatment every few years. Current EULAR recommendations (276) for treatment of RA focused on early treatment and treat-to-target approach; the ACR guidelines are similar.(277) Early treatment means that therapy with DMARDs should be initiated as soon as the diagnosis of RA is made. Treat-to-target implies that treatment should be aimed at reaching a target of remission or low disease activity in every patient. The treat-to-target approach strategy consists of treating and adapting therapy as needed to improve a disease activity index of at least 50% within 3 months and thus to have more than a 50% probability of reaching low disease activity or remission at 6 months.(278) Attaining remission will prevent joint destruction or at least progression of joint damage,(279, 280) optimise physical function, improve quality of life and work capacity (281, 282) and reduce comorbidity risks.(283, 284) Today, it is widely accepted that clinical remission (especially in early RA) is the primary therapeutic target for people with RA, with low disease activity (in established RA if remission is not achievable) as the best possible alternative.(285) Low disease activity or remission is currently a realistic goal for more than 75% to 80% of people with RA.(276)

As shown in Figure 3.1, the guidelines state that treatment should be initiated with a (combination of) conventional synthetic DMARDs for newly diagnosed patients, of which methotrexate should be part.(275) Low dose glucocorticoids should be considered part of the initial treatment strategy for up to 6 months but should be tapered as rapidly as clinically feasible.(276) In case the treatment target is not achieved with the first DMARD strategy, guidelines recommend the addition of a bDMARD if poor prognostic factors are present. In the absence of such factors, another conventional synthetic DMARD strategy

should be attempted first. If a first bDMARD has failed, patients should be treated with another bDMARD.(276)

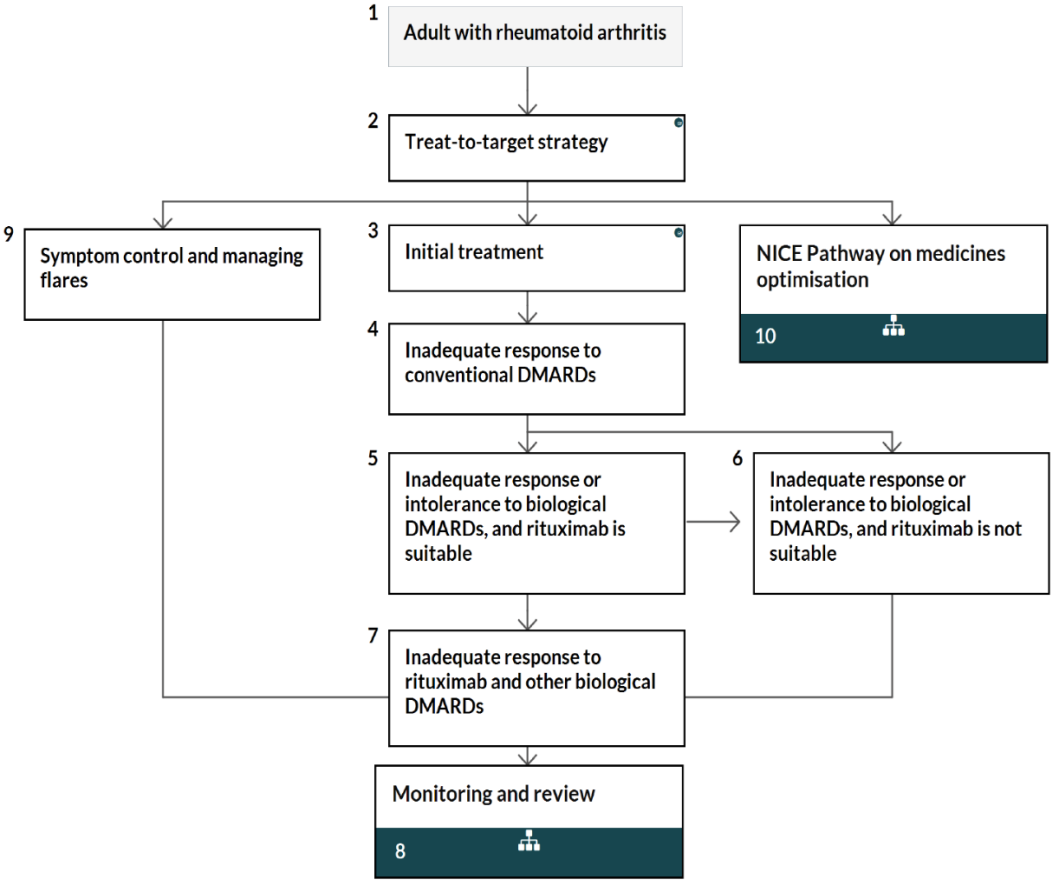


Figure 3.1 Management of rheumatoid arthritis, adopted from the National Institute for Health and Care Excellence (NICE) guideline (275)

The management of RA has changed dramatically over the past 30 to 40 years. Few therapeutic agents existed then, which were either minimally or not efficacious, because of toxicity and the fact that optimal dosing and onset of action had not yet been elucidated for some agents.(286-288) Over the past two decades, significant progress has been made regarding the understanding of disease pathophysiology, optimal outcome measures, and effective treatment strategies, including identifying cytokines that promote synovial inflammation (e.g. tumour necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor and interleukin-6) and treating RA early.(289) The optimal use of

DMARDs, in particular the anchor DMARD methotrexate,(288, 290, 291) and the availability of new bDMARDs,(292, 293) have dramatically enhanced the success of RA management.

Nevertheless, unlike other continents, bDMARDs penetration is still very low in Africa. Only South Africa, Kenya and North African countries have access to many of the bDMARDs that are available as these are also countries with robust health insurance schemes.(227) Particularly in sub-Saharan Africa, the low penetrance is caused by the non-availability of bDMARDs and the lack of affordability. As a result, When patients seek conventional healthcare, they are often seen at community health centres and receive symptomatic treatment only, such as NSAIDs or steroid for pain relief.(227)

3.3.1 Comorbidities or Coexisting Long-Term Conditions

Comorbidities are frequent and may shorten the lifespan of people with RA.(134, 214, 215) Currently, National Institute for Health and Care Excellence (NICE) guidelines for the management of RA suggests annual checks for the development of hypertension, ischaemic heart disease, osteoporosis and depression.(275) In addition, EULAR published recommendations for screening and managing selected comorbidities in RA patients, including cardiovascular diseases, cancer, infections, gastrointestinal diseases, osteoporosis and depression.(294) These comorbidities are essential to consider because they are frequently observed in RA and impact on health and quality of life outcomes.(217-219, 295)

An international cross-sectional study assessing comorbidities in people with RA found depression to be the most frequent comorbidity, affecting 15% of patients; gastrointestinal ulceration was reported in 10.8% of patients, cardiovascular diseases in 6% of patients, and cancer in 4.5% of patients.(296) People with RA have been shown to have a 3.2 times

higher risk of myocardial infarction leading to hospitalisation and almost 6 times higher risk of a silent myocardial infarction than the general population.(134) In RA, the risk of myocardial infarction is similar to that of people with diabetes.(297) There is also a slightly increased risk of cancer (standardised incidence rate, 1.05; 95%CI 1.01-1.09) compared with the general population. This increased risk appears to be due to specific cancers: lymphoma, lung cancer, and skin cancer.(134) Infections and tuberculosis are also increased in RA patients and may be treatment related (for example, corticosteroids and TNF inhibitors have been shown to increase the risk of tuberculosis) (217, 298-300) while gastric ulcers may result from the use of non-steroidal anti-inflammatory drugs.(134) Also, increased risks of hip fracture and osteoporosis in RA have been reported approximately twice higher than those without RA.(301, 302) Meta-analyses revealed the prevalence of major depressive disorder to be 16.8% (95%CI 10-24%), while the prevalence of depression was 38.8% (95%CI 34-43%). Depression is highly prevalent in RA and associated with poorer RA outcomes.(303)

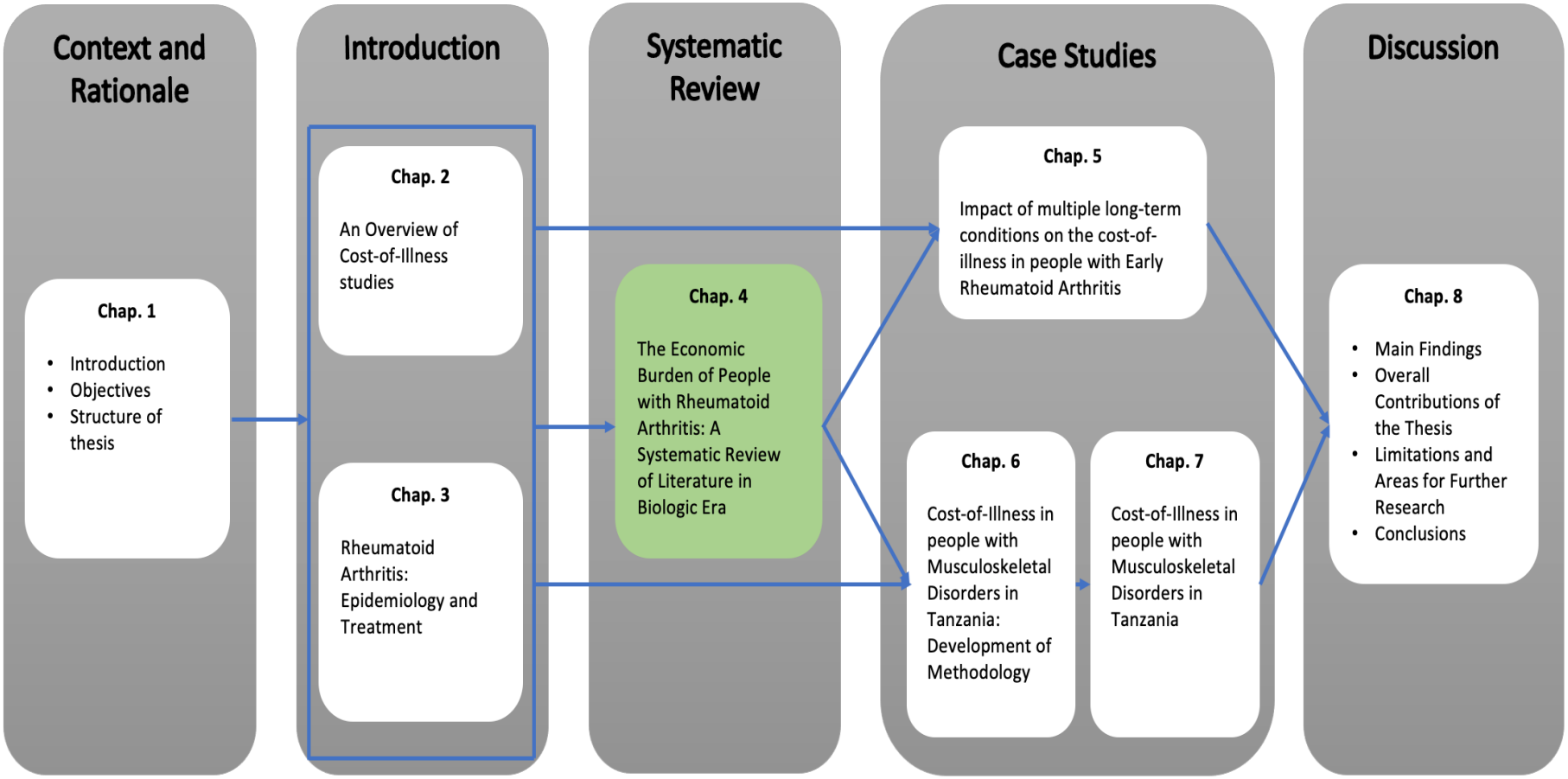
3.4 Chapter Summary

RA is a well-researched health condition with many advances in effective treatment options. However, as with most clinical/health research on chronic disease, the focus had been on improving clinical outcomes. In recent years, there has been growing recognition of the importance of patient-reported outcome measures.(304, 305)

In the high-income setting, patients are becoming increasingly involved in the decision-making process for the management of their conditions.(306, 307) What we are beginning to learn from them are outcomes beyond clinical and health measures that are important to them. This is evident from several of EULAR's initiatives and recommendations on including work participation as relevant outcome measure.(276, 304, 305)

In an LMIC setting, the challenges more significant. This relates to health inequality, such as political instabilities, wars, low income, unemployment, and lack of health personnel. These in turn contribute to poor nutrition, housing, sanitation, and education.(225) In addition, bDMARDs are still non-available and unaffordable in most African countries, particularly in sub-Saharan Africa. When patients seek conventional healthcare, they often receive symptomatic treatment only, such as NSAIDs or steroids for pain relief.

Because of this shift in how we approach chronic diseases in medical research, it is pertinent that we also think about how this impacts the way we look at COI. These issues are highly relevant in estimating COI. The next chapter will undertake a systematic review of COI studies in RA in the biologic era to understand how COI has been measured in contemporary literature and also how COI in RA has evolved in the past two decades.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CHAPTER 4. THE ECONOMIC BUDREN OF PEOPLE WITH RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW OF LITERATURE

4.1 Introduction

As described in Chapter 3, there have been major advances in rheumatoid arthritis (RA) management over the past decades. The identification of cytokines that promote synovial inflammation (e.g. tumour necrosis factor, granulocyte-macrophage colony-stimulating factor and interleukin-6) led to therapeutics that target the disease process itself.(308) The introduction of biologic disease-modifying antirheumatic drugs (DMARDs) in the late 1990s offered potent options for patients with inadequate response to conventional synthetic DMARDs. However, these targeted therapies are significantly more expensive than the previous conventional DMARDs and have impacted scarce healthcare resources.

In 2000, two systematic reviews for COI studies in RA were published,(309, 310) including COI studies published between 1978 and 1998. Although cost categories and estimated costs varied in direct costs, both reviews concluded that hospitalisation was the main cost driver, where costs for medication represented a comparatively small proportion of direct costs. When assessed, indirect costs were usually calculated as annual sick leave and ranged from 3 to 30 days. It was believed that indirect costs substantially exceeded direct costs; however, the evidence for this assessment was not sufficient, though several studies showed they were more significant.(310)

Since the introduction of biologics, a literature review by Boonen et al. in 2011 (47) indicated that more than two-thirds of the direct cost was attributable to outpatient costs, of which the major contribution was from drug costs. More recently, Hresko et al. focused on studies of direct medical costs associated with RA patients in the United States,(311) total direct medical costs for all RA patients using any treatment regimen were estimated to be

$12,500 per year among the 12 studies. In contrast, the costs increased to $36,000 per year for patients receiving biologics. For indirect costs, studies generally focus on absenteeism associated with the diseases. The systematic review for indirect costs due to RA by Burton et al.(93) indicated that an apparent decrease in the prevalence of work disability due to RA since the 1970s may be related to a decrease in physically demanding work rather than to epidemiologic changes in RA. More recent reviews (312, 313) suggested that the human capital approach (HCA) is the most commonly used method for valuing productivity costs, while indirect costs valued by the HCA were 3 to 10 times higher than the friction costs approach (FCA). To date, there is still limited research on presenteeism or productivity loss to caregivers, both of which may present a substantial economic strain.

Over the past few decades, COI studies in RA showed the major cost component in direct costs has gradually shifted from hospitalisation to medication.(47, 309-311) However, while indirect costs could contribute to a large proportion of total costs, the methods used to calculate indirect costs significantly impact the results. Moreover, whenever the reviews were performed (i.e. before or after the introduction of biologics), all suggested the high degree of uncertainty in COI estimates and the large variations in cost estimates.(47, 309, 310, 312, 314-316) Therefore, there is a need to perform a comprehensive systematic review for COI studies in RA since the introduction of biologics to address this evidence gap.

4.2 Objectives

To address the first Objective formulated in Chapter 1, the aim of this systematic review was to map the existing evidence on COI of RA. In particular, this review examined how costs have been measured and estimated, as well as assembled and interpreted based on available data.

4.3 Methods

The systematic review was carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (317) and registered on PROSPERO (registered number: CRD42018085227). Given healthcare and related costs vary across different countries and healthcare systems. A single estimate of global COI would not be meaningful or applicable across different settings. This systematic review has focused on the similarities and differences across these studies and how these impact the overall COI. Therefore, the Synthesis Without Meta-analysis (SWiM) checklist [12] was adopted to ensure the robustness of the synthesis approach in this review.

4.3.1 Eligibility Criteria

Studies were included if they met the following criteria: (1) population included adult patients diagnosed with RA; (2) cost associated with RA were measured or estimated, such as direct costs, indirect costs or both. Because COI studies are descriptive analyses the economic burden of health problems on a population, trials were not included in this systematic review. Due to the introduction of first biologics in the late 90s and the subsequent evolution of the treatment pathway, only studies from 2000 onwards were included.

4.3.2 Databases and Search Strategy

A comprehensive search was carried out on Ovid MEDLINE and EMBASE (January 1, 2000 to February 22, 2019). In addition to search terms relating to RA, a search filter (318) for economic studies was also used to capture potentially relevant studies (Appendix A). The search was restricted to English language studies only.

4.3.3 Data Extraction

The titles and abstracts of all retrieved studies were screened, and full texts of all potentially eligible articles were reviewed in detail. A data extraction form was developed and pilot-tested on a randomly selected subsection of studies, including patient characteristics, costs (and its breakdown when reported), setting, methodologies, main findings and limitations. Other essential characteristics of quality appraisal criteria (source of funding, conflict of interest) were also included. To ensure a comprehensive data extraction process and optimise the usability of the extraction form, the extraction form was amended based on outcomes and feedbacks during the pilot testing phase. A random sample of 50% of studies was validated independently by a second reviewer within this PhD supervisory team.

4.3.4 Quality Assessment

Modified CHEERS Checklist

In the absence of a quality assessment tool for COI studies, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (319) (Appendix B) was modified to evaluate the quality of included studies. The CHEERS checklist is designed to assess reporting quality of economic evaluations, such as cost-effectiveness or cost-utility analyses. Esitmating the incremental per-patient cost of specific health interventions is quite a different task from estimating the overall societal costs of health conditions in COI studies. Therefore, items specific to economic evaluation, such as comparator, outcome measurement, and effectiveness are replaced by population (optional for studies with matched populations), cost components, and cost. Moreover, items regarding choice of model, assumptions and parameters are kept as optional for few COI studies use model-based approach.

The modified CHEERS checklist has 21 items, including clear description of the context, research question and its relevance for the health policy or practice, characteristics of the population, study perspective, matched population (optional), time horizon, cost components, valuing approaches, choice of model, assumptions and parameters (optional for model-based approach), analytical methods, estimated costs, characterising uncertainty and heterogeneity, discussion of study findings, limitations, generalisability and current knowledge, and lastly source of funding and conflict of interest. The assessment of each item was presented individually in the result.

4.3.5 Statistical Analysis

The estimated total COI was evaluated according to study characteristics and expressed in their cost compositions of direct or indirect costs if reported. All absolute costs were converted to US dollars, inflated to 2017 levels and adjusted for buying power using purchasing power parities to facilitate comparison. For studies, where the cost year was not reported, the last year of the enrolment period was used. Data were entered into a Microsoft Excel spreadsheet and analysed using R V3.5.2.

In order to determine if there was an increasing or decreasing trend in the proportion of drug costs and inpatient costs of overall direct costs, the Cochran-Armitage test for linear trend in proportions was used.(320) The Cochran–Armitage test for trend assesses whether there is a monotonically increasing or decreasing trend in the proportions with a positive outcome or response over the C-ordered categories of an ordinal independent variable. The proportion of drug costs and inpatient costs of direct costs were applied to test the statistical significance for increasing or decreasing trend chronologically.

4.4 Results

A total of 2,981 studies were identified in the initial literature retrieval. 2,925 studies were obtained after excluding duplicates. Of the title and abstract screened, 151 studies were ordered as full papers and assessed in detail. Among the 151 studies assessed for eligibility, 60 studies were excluded because of not fulfilling the definition of COI studies, for example, cost-effectiveness analyses or only limited to treatment costs. Finally, 72 studies met the inclusion criteria (Figure 4.1).

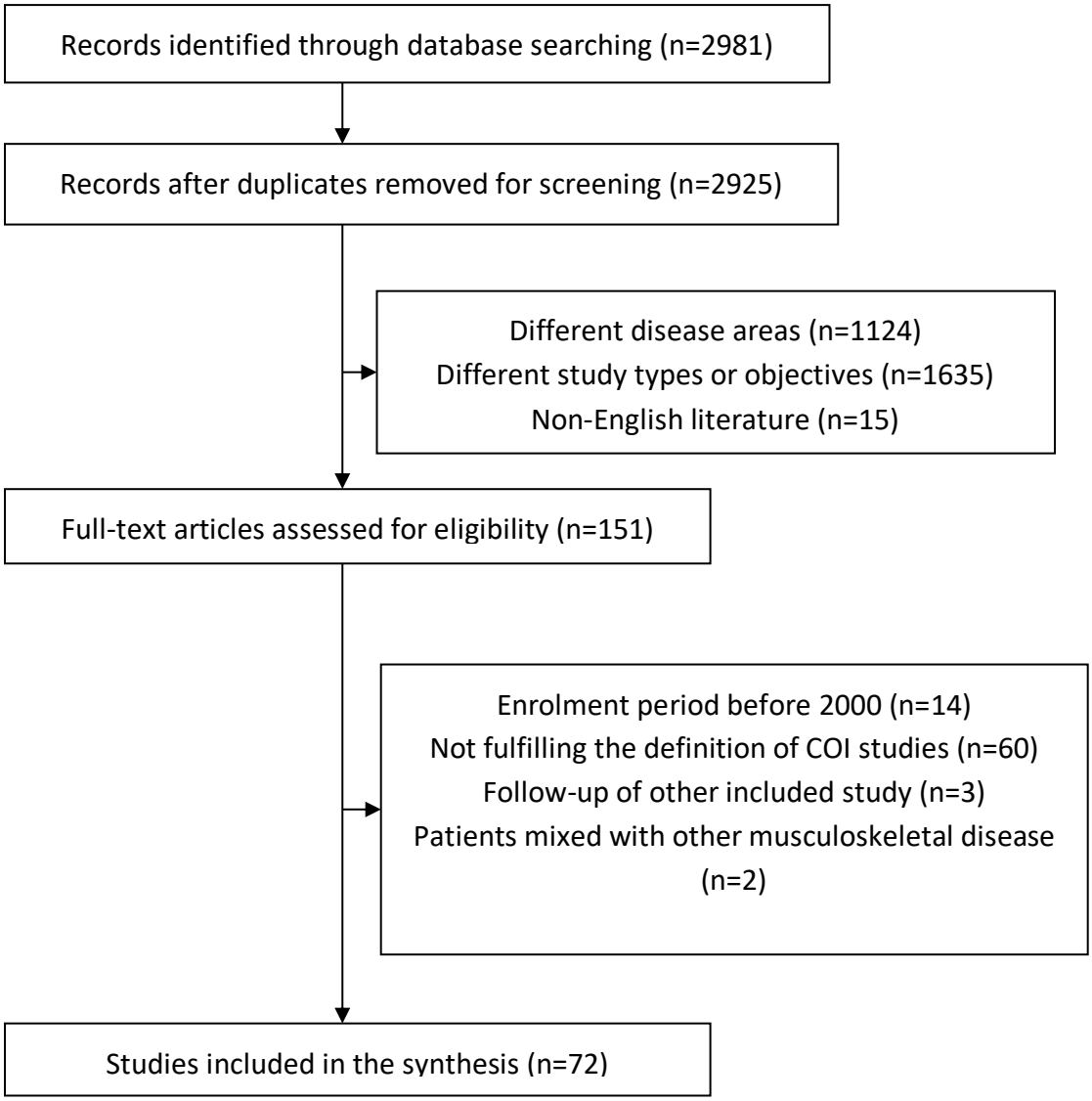


Figure 4.1 PRISMA flow diagram

4.4.1 Study characteristics

Overall, studies estimated the COI of RA in 28 countries (Appendix C). The majority were conducted in Europe (n=34; 47.2%), followed by North America (n=19; 26.4%), Asia (n=15; 20.8%), Latin America (n=3; 4.2%), and Australasia (n=1; 1.4%). Among the studies, females accounted for the main composition of population ranging from 57.5% to 95.6% among studies. The mean age of participants ranged from 46 to 63 years old. The mean duration of disease among participants ranged from the onset of disease to 25.9 years.

4.4.2 Methodological Approaches

In the majority of the studies, the data sources were retrospective databases (n=61; 84.7%), including health insurance databases, disease registries, and hospital administrative records, followed by self-reported questionnaire surveys (n=10; 13.8%). One study estimated costs using a simulation modelling approach.(321) COI estimates were estimated from different perspectives – that of the society (n=32; 44.4%), payers (n=14; 19.4%), patients (n=2; 2.8%), and employers (n=3; 4.2%); 21 studies (29.2%) did not report perspective. Overall, the majority of included studies (n=58; 80.5%) were carried out using a prevalence-based approach. The studies that adopted the incidence-based approach, focused on recent-onset patients and were primarily conducted in a European setting.(322-329)

Cost components and measurement of direct or indirect costs also varied markedly due to the aims and data availability among studies. Table 4.1 presented cost components included in direct costs. In estimating direct costs, multiple cost components were included in the estimates. Most commonly, these consisted of drug costs, hospitalisation, outpatient attendance (including costs of visiting different healthcare professionals), and various other healthcare-related costs (including diagnosis, devices and adaptation to homes/cars,

transportation and informal care). However, costs for diagnostic examination, device and adaptation, and non-medical costs were less commonly included in studies conducted in North America, Asia and Australia. The cost of informal care was only available in a limited number of studies, which indicated it could contribute to a significant proportion in direct costs.(328-330)

For estimating indirect costs, absenteeism and work disability were the major cost components of indirect costs, although the definitions varied among studies as presented in Table 4.2. The measurements of sick leave, work hour loss, and short-term work disability were the most commonly reported items in terms of absenteeism; receiving disability pension and early retirement were categorised as work disability. Others included presenteeism, unemployment due to RA, unpaid work or non-marketplace activities, and third-party help. The HCA was the most commonly used approach to estimating indirect costs when reported, whereas two study only used the FCA.(331, 332) Six studies used both approaches.(324, 333-337) The remaining 11 studies did not report their approach.

Overall, 27 studies reported both direct and indirect costs, while 36 and nine reported only direct and indirect costs, respectively. The following sections are presented based on this arrangement to avoid cross-reporting of studies that reported both direct and indirect costs.

Table 4.1 Cost components included in direct costs among studies

Author	Country	Cost year	Medication	Inpatient[a]	Outpatient[b]	Diagnostic examination[c]	Devices and adaptation	Non-medical[d]
Europe								
Radner et al. 2014	Austria	NR	+	+	+	+	+	+
Westhovens et al. 2005	Belgium	2000	+	+	+		+	+
Klimes et al. 2014	Czech	2013	+	+	+	+		
Loppenthin et al. 2018	Denmark	2006	+	+	+			
Flipon et al. 2009	France	2003	+	+	+	+		+
Kobelt et al. 2008	France	2005	+	+	+	+	+	+
Chevreul et al. 2014	France	2007	+	+	+	+		+
Beresniak et al. 2011	France	2008		+	+	+	+	+
Fautrel et al. 2016	France	2010	+	+	+	+	+	+
Beck et al. 2015	France	2012	+	+	+	+		+
Ruof et al. 2003	Germany	2001	+	+	+	+	+	+
Kirchhoff et al. 2011	Germany	2002	+	+	+			+
Hulsemann et al. 2005	Germany	2004	+	+	+		+	+
Huscher et al. 2015	Germany	2011	+	+	+	+		
Ziegelbauer et al. 2018	Germany	NR	+	+	+			
Horvath Cs et al. 2014	Hungary	2012		+	+			
Della Rossa et al. 2010	Italy	NR	+		+	+		+
Verstappen et al. 2007	Netherlands	2003	+	+	+	+	+	+
Kvamme et al. 2012	Norway	2010	+	+	+	+		
Miranda et al. 2012	Portugal	2010	+	+	+	+	+	+
Leon et al. 2016	Spain	2010	+	+	+	+		+
Jacobsson et al. 2007	Sweden	2004	+	+	+		+	+

Author	Country	Cost year	Medication	Inpatient[a]	Outpatient[b]	Diagnostic examination[c]	Devices and adaptation	Non-medical[d]
Eriksson et al. 2015	Sweden	2010	+	+	+			
Hallert et al. 2014	Sweden	2012	+	+	+	+		
Johansson et al. 2015	Sweden	2012	+	+	+			
Hallert et al. 2016	Sweden	2013	+	+	+	+		
Malhan et al. 2010	Turkey	NR	+	+	+	+	+	
Malhan et al. 2012	Turkey	2011	+	+	+			
Baser et al. 2013	Turkey	NR	+	+	+	+	+	+
North America								
Fautrel et al. 2007	Canada	2002	+	+	+	+	+	
Tarride et al. 2013	Canada	2002		+	+	+		
Barnabe et al. 2013	Canada	2008		+	+			
Ohinmaa et al. 2014	Canada	2008		+	+			
Yelin et al. 2007	USA	2003	+	+	+		+	+
Kessler et al. 2008	USA	2005	+	+	+			
Birnbaum et al. 2010	USA	2005	+	+	+		+	+
Joyce et al. 2009	USA	2006	+	+	+	+		
Kawatkar et al. 2012	USA	2008	+	+	+			+
Bonafede et al. 2012	USA	NR	+	+	+			+
Simons et al. 2012	USA	NR	+	+	+		+	+
Kleinman et al. 2013	USA	2010	+	+	+			
Chen et al. 2018	USA	2013	+	+	+			
Zhou et al. 2016	USA	2012	+	+	+			
Grabner et al. 2017	USA	2014	+	+	+	+		
Strand et al. 2018	USA	2014	+	+	+	+		+

Author	Country	Cost year	Medication	Inpatient[a]	Outpatient[b]	Diagnostic examination[c]	Devices and adaptation	Non-medical[d]
Curtis et al. 2017	USA	2016	+	+	+			
Asia								
Aggarwal et al. 2006	India	NR	+	+		+		+
Xu et al. 2014	China	2005	+	+	+	+		+
Hu et al. 2017	China	2013	+	+	+			
Lee et al. 2007	Hong Kong	2003	+	+	+	+		
Zhu et al. 2011	Hong Kong	2006	+	+	+	+	+	+
Tanaka et al. 2010	Japan	2007	+		+	+	+	
Tanaka et al. 2013	Japan	2007	+	+	+		+	+
Sruamsiri et al. 2018	Japan	2016	+	+	+			
Kwon et al. 2012	S. Korea	2009	+	+	+	+		
Lang et al. 2016	Taiwan	2011	+	+	+			
Wang et al. 2016	Taiwan	2011	+	+		+	+	
Shi et al. 2018	Taiwan	2016	+	+	+			
Osiri et al. 2007	Thailand	2001	+	+	+	+	+	+
Osiri et al. 2013	Thailand	2009	+		+	+		
Latin America								
Chermont et al. 2008	Brazil	2002	+	+	+	+	+	+
Alvarez-H et al. 2012	Mexico	2005	+	+	+	+	+	+
Australasia								
Cross et al. 2006	Australia	NR	+	+	+	+	+	

[a] Inpatient costs include costs of hospitalisation, surgery, and emergency room visit; [b] Outpatient costs include costs of visits to physicians and other healthcare professionals, such as nurse, OT, PT etc.; [c] Diagnostic examination includes costs of imaging and laboratory test; [d] Non-medical costs include costs of informal care, home help, and transportation etc.

Table 4.2 Methods and cost components included in indirect costs among studies

Author	Country	Cost year	Method	Absenteeism[a]	Work disability[b]	Others
Europe						
Radner et al. 2014	Austria	NR	HCA/FCA	+	+	
Kruntoradova et al. 2014	Czech	2010	FCA	+	+	Productivity impairment
Klimes et al. 2014	Czech	2013	FCA	+	+	
Loppenthin et al. 2018	Denmark	2006	NR	+	+	Foregone earnings
Sogaard et al. 2010	Denmark	2007	HCA	+		Presenteeism
Martikainen et al. 2016	Finland	2013	HCA	+	+	
Flipon et al. 2009	France	2003	NR		+	
Kobelt et al. 2008	France	2005	HCA	+	+	
Merkesdal et al. 2005	Germany	2001	HCA/FCA	+	+	
Kirchhoff et al. 2011	Germany	2002	HCA/FCA	+	+	Work loss
Ruof et al. 2003	Germany	2003	NR	+	+	
Huscher et al. 2015	Germany	2011	HCA/FCA	+	+	
Della Rossa et al. 2010	Italy	NR	HCA	+		
Kvamme et al. 2012	Norway	2010	HCA/FCA	+		
Malinowski et al. 2016	Poland	2012	HCA	+	+	
Miranda et al. 2012	Portugal	2010	HCA	+		Work day lost by the companion
Jacobsson et al. 2007	Sweden	2004	NR	+	+	Loss of leisure time
Eriksson et al. 2015	Sweden	2010	HCA/FCA	+	+	
Hallert et al. 2014	Sweden	2012	HCA	+	+	
Hallert et al. 2016	Sweden	2013	HCA	+	+	
Malhan et al. 2012	Turkey	2011	HCA	+	+	
North America						
Fautrel et al. 2007	Canada	2002	HCA/WTP			
Thanh et al. 2013	Canada	2010	HCA	+		
Birnbaum et al. 2010	USA	2005	NR	+	+	
Simons et al. 2012	USA	NR	NR	+		Workforce participation/ income loss

Author	Country	Cost year	Method	Absenteeism[a]	Work disability[b]	Others
Gunnarsson et al. 2015	USA	2008	NR	+		
Kleinman et al. 2013	USA	2010	NR	+	+	
Strand et al. 2018	USA	2014	HCA	+		
Asia						
Xu et al. 2014	China	2005	HCA	+		
Hu et al. 2017	China	2013	HCA	+		
Zhu et al. 2011	Hong Kong	2006	HCA	+		Unemployment/ days off from household work or daily activities
Sruamsiri et al. 2017	Japan	2016	NR	+		Presenteeism
Wang et al. 2016	Taiwan	2011	NR	+		Presenteeism
Osiri et al. 2007	Thailand	2001	NR	+		
Latin America						
De Azevedo et al. 2008	Brazil	2005	HCA	+		
Alvarez-Hernandez et al. 2012	Mexico	2005	NR			Job loss/ third party help

Abbreviations: HCA, human capital approach; FCA, friction cost approach; WTP, willingness to pay.

[a] Absenteeism includes the costs of work hour loss, short-term and long-term sick leaves.

[b] Work disability includes the costs of early retirement and disability pensions.

4.4.3 Direct Costs

The annual estimates of direct costs of people with RA ranged from $401 to $67,306 in the 36 studies that reported direct costs. Of these, 22 studies included these common cost components (Figure 4.2), i.e. drug costs, hospitalisation and outpatient attendance. Except for two studies with different patient characteristics (newly-diagnosed patients (322) and elderly population (338)), drug costs contributed to between 9.8% and 87.2% of direct costs. Although drug costs comprised the main component of direct costs, no statistically significant increasing trend was found (p = 0.647, Table 4.3). However, the proportion of costs for hospitalisation showed a statistically significant decrease over time (p = 0.044).

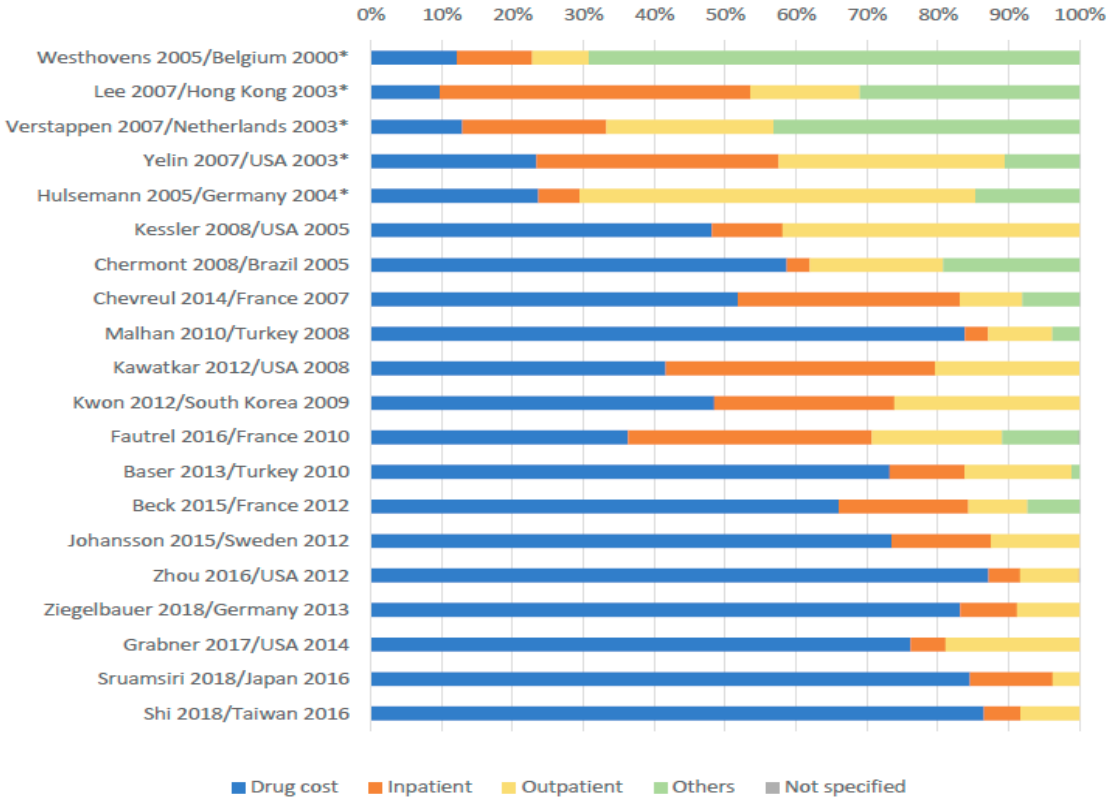


Figure 4.2 Distribution of cost components in direct costs of RA chronologically

Costs incurred from visits to other healthcare professionals, such as nurse, physical therapist, and occupational therapist, that were measured separately in some studies,(323, 325, 326, 328, 329, 334, 335, 339-349) were summarised as "Outpatient". Costs for diagnostic tests, devices and adaptation, transportation and informal care were categorised as "Others".
*Drug costs were not the largest contributor to direct costs.

Table 4.3 The Cochran-Armitage test for linear trend analysis in proportions of drug costs and hospitalisation costs

Cost component	Proportion of direct costs (correlation structure)	One sided test	Test statistic	
	(ρ1, ρ2, ρ3, ρ4, ρ5 ... ρ20)		Z	P value
Drug	(0.122, 0.098, 0.130, 0.234, 0.237)	Increasing	0.376	0.647
	(0.482, 0.588, 0.599, 0.838, 0.417)			
	(0.485, 0.364, 0.732, 0.661, 0.735)	Decreasing		0.353
	(0.872, 0.832, 0.762, 0.846, 0.865)			
Hospitalisation	(0.106, 0.438, 0.203, 0.342, 0.058)	Increasing	1.706	0.956
	(0.099, 0.032, 0.313, 0.033, 0.380)			
	(0.254, 0.344, 0.106, 0.183, 0.140)	Decreasing		0.044*
	(0.044, 0.080, 0.049, 0.116, 0.052)			

4.4.4 Indirect Costs

Nine of the 72 studies were specifically on indirect costs, of which only 4 studies (337, 350-352) provided a breakdown of cost components (Table 4.4). With heterogeneous definitions in the limited number of studies, it is challenging to compare cost composition. Presenteeism, while rarely estimated in studies, accounted for 8.8% and 92.9% of indirect costs in a Danish and Japanese study, respectively.(351, 353) Overall, annual estimates of indirect costs ranged from $595 to $22,444 in the 9 studies reporting indirect costs.

Table 4.4 Measurements of cost components in indirect cost of RA

Reference	Absenteeism	Work disability	Others
Malinowski (350)	short-term/long-term/ permanent work disability	NA	NA
Sogaard (351)	work hour loss/sick leave	NA	presenteeism
Sruamsiri (353)	work hour loss	NA	presenteeism
Merkesdal (337)	sick leave	disability payment from cessation of work	NA

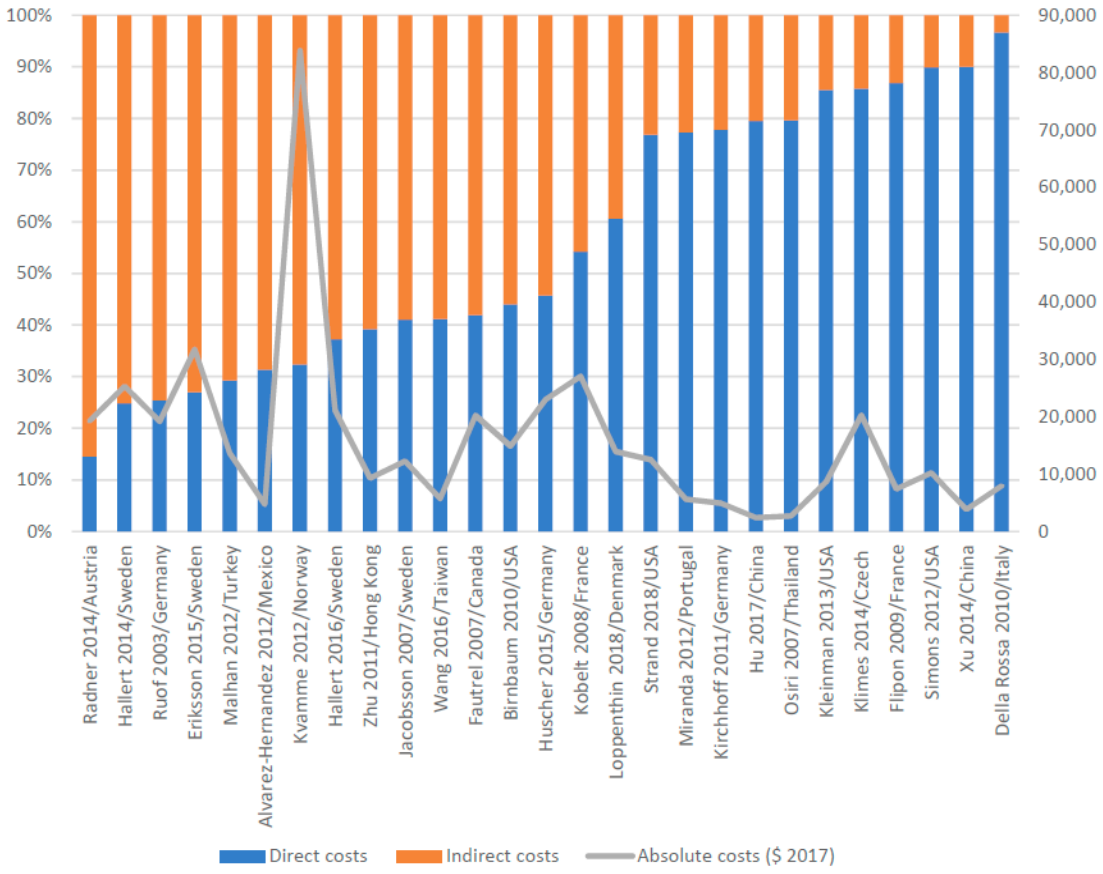


Figure 4.3 Distribution between direct and indirect costs in total costs of RA

4.4.5 Direct and Indirect Costs of RA

Overall, 27 studies included both direct and indirect costs as presented in Figure 4.3. The annual estimates of combined direct and indirect costs ranged from $2,408 to $83,845; the majority of the estimates were in the range of $10,000 to $30,000. One outlier was observed – a study conducted in Norway;(335) in which the high monetary value was due to the subgroup on biologic treatments as well as a high proportion of indirect costs accounting for 67.7%.

In terms of the composition of direct and indirect costs, the approach to estimating indirect costs had an important impact. For studies where indirect costs dominated, it was observed that work disability measured by disability pension was taken into account in these studies,(324-326, 336, 344) except for two studies from Mexico and Hong Kong,(354,

355) where indirect costs were driven by unemployment due to RA. On the other hand, for those studies where direct costs dominated, work disability was generally not included as an indirect cost component.(106, 333, 345, 356-358) Indirect costs mainly consisted of sickness absence, resulting in a lower percentage of indirect costs. In addition, these studies have relatively lower annual estimates of absolute costs (<$10,000) in common. With the exception of studies in which indirect costs mainly consisted of sickness absence, indirect costs accounted from 39.4% to 85.5% total costs in the biologic era. Estimates using the HCA were 1.5 to 4.4 times higher than those using FCA in those studies that adopted both approaches.

4.4.6 Quality Assessment

Overall studies scored well against the 21 criteria of the modified CHEERS checklist (and Table 4.5 and Figure 4.4). Most studies clearly described the study context, objectives, population, time horizon, cost components, analytical methods, currency or price conversion, estimated costs and discussion. However, only 59% of studies stated their study perspectives, and approximately 70% addressed the uncertainty and heterogeneity. In addition, 76% and 63% of studies reported the source of funding and conflict of interest, respectively.

Table 4.5 Quality assessment by modified CHEERS checklist

Recommendations	Yes	No	Not applicable	%
1. Title	67	5	0	93%
2. Abstract	59	13	0	82%
3. Background and objectives	69	3	0	96%
4. Target population and subgroups	62	9	0	87%
5. Setting and location	71	1	0	99%
6. Study perspective	50	22	0	59%
7. Population (optional)	12	0	60	17%
8. Time horizon	67	5	0	93%
9. Cost components	61	11	0	85%
10. Estimating resources and costs	70	2	0	97%
11. Currency, price date, and conversion	63	9	0	88%
12. Choice of model (optional)	1	0	71	1%
13. Assumptions (optional)	1	0	71	1%
14. Analytical methods	57	15	0	79%
15. Study parameters (optional)	1	0	71	1%
16. Cost	72	0	0	100%
17. Characterising uncertainty	51	21	0	71%
18. Characterising heterogeneity	52	20	0	72%
19. Study findings, limitations, generalisability, and current knowledge	68	4	0	94%
20. Source of funding	55	17	0	76%
21. Conflicts of interest	45	27	0	63%

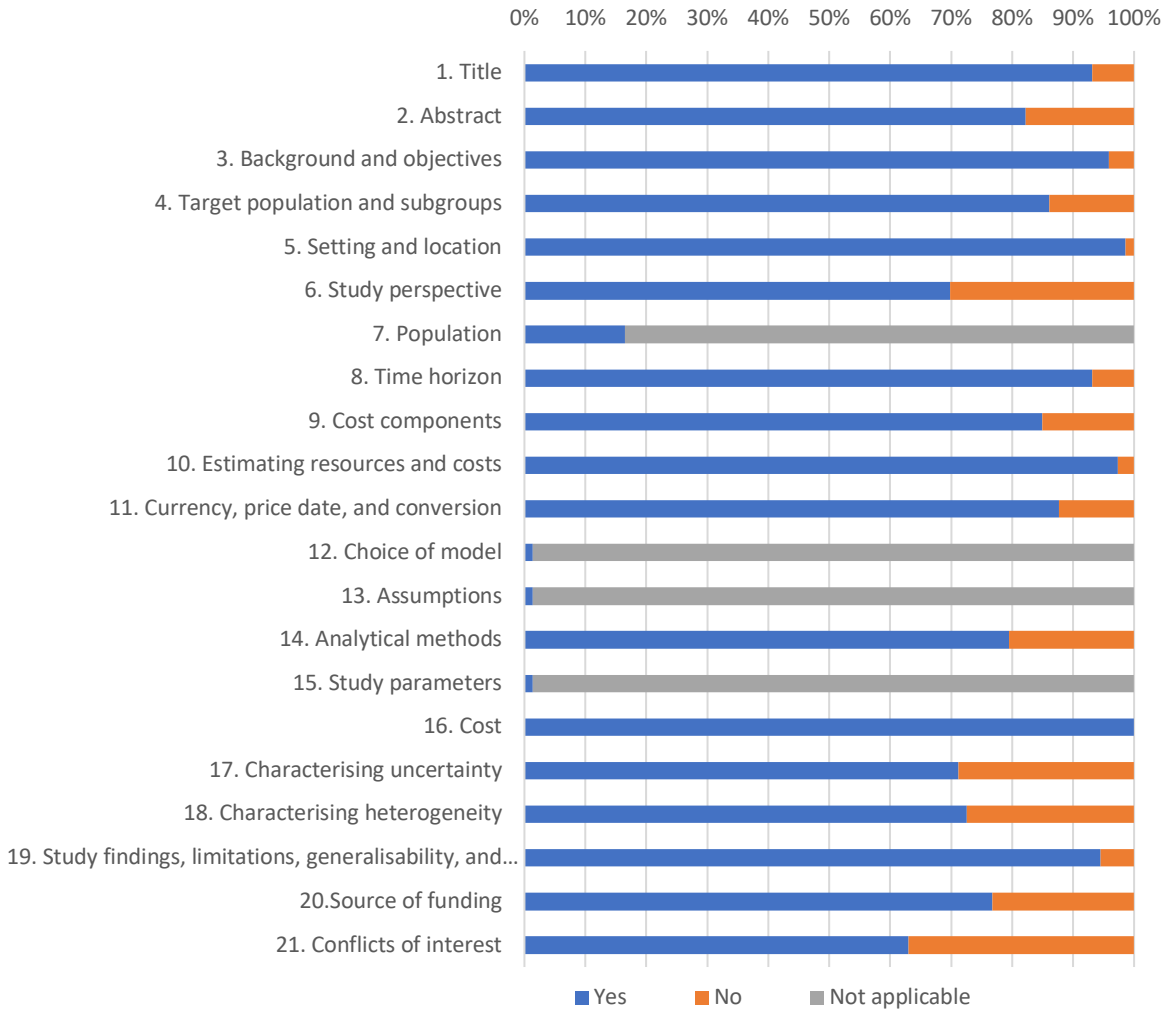


Figure 4.4 Bar chart illustrating quality assessment of included studies by using modified CHEERS checklist, as percentage of adequately reported items

4.5 Discussion

The aim of this systematic review was to examine how cost components have been measured and estimated in COI studies of RA in the biologic era, so as to assemble and appropriately interpret available data. Results included 72 studies that were conducted in 28 countries, with differences in populations, healthcare systems, cost estimates, and methodologies across and within countries. The variety in methodologies might be due to different study purposes as well as data availability. The prevalence-based approach provides a snapshot on the economic burden of RA to the society, while the incidence-based approach aims to estimate from the onset of disease, and therefore, requires longitudinal data. Also, most studies conducted retrospective analyses from claim databases or disease registries rather than developing a dedicated primary data collection. The majority of included studies estimated costs directly and entirely attributed to RA, whereas few studies measured all expenditures incurred by people with RA or incremental costs by using matched-control or regression-based approaches.

On visual inspection, the proportion of drug costs, as the main component contributing to direct costs, was increasing over time. Although no statistically significant increase in this trend could be established. However, the statistically significant decrease in the proportion of costs for hospitalisation suggests that costs have shifted to other components of direct costs. These results need to be interpreted with caution though due to the small sample size. The cost of informal care was only available in a limited number of studies, which indicated it could contribute to a significant proportion in direct costs.(328-330)

Absenteeism and work disability were the most commonly reported components for indirect costs. Work disability, which mainly included pay-outs for disability pensions, was identified as the key cost driver of indirect costs. While absenteeism and work disability are relatively straightforward to measure, presenteeism is still rarely addressed

and lacks a clear measurement methodology.(359, 360) The proportion of presenteeism in indirect costs varied substantially (8.8%, 92.9%)(351, 353) Regarding the valuing approach, although HCA was more commonly used, this approach has been criticised as possibly over-estimating actual indirect costs, while the FCA is relatively difficult to implement as it requires detailed information or assumptions.(82) The findings suggested that the HCA was the most commonly used approach when reported, whereas two studies only used the FCA.(331, 332) Among the six studies adopting both approaches,(324, 333-337) the FCA usually served as an alternative approach in the sensitivity analysis. Estimates using the HCA were 1.5 to 4.4 times higher than those using FCA in those studies that adopted both approaches. However, the remaining 11 studies did not report their approach.

Where indirect costs dominated in those studies that reported both direct and indirect costs, the approach to estimating indirect costs had a significant impact. For studies where indirect costs dominated, it was observed that work disability measured by disability pension was taken into account in these studies,(324-326, 336, 344) except for two studies from Mexico and Hong Kong, (354, 355) where indirect costs were driven by unemployment due to RA. On the other hand, for those studies where direct costs dominated, work disability was generally not included as an indirect cost component.(106, 333, 345, 356-358) In the studies measuring work disability rather than considering sickness absence only, indirect costs contributed a much larger proportion than direct costs, and also resulted in relatively higher monetary values.

Since the introduction of the first biologic (etanercept) in 1998 in the US and subsequent wide adoption of early and intensive treatment strategies, the composition of total costs of RA has been transformed. In an earlier systematic review conducted by Rat et al,(316) direct costs accounted for 25% to over 50% of the total cost among the included studies

between 1978-2002. In addition, costs associated with inpatient care contributed up to 75% of direct costs. Our findings from included studies from 2000 onwards indicated that drug costs comprised the main cost component of direct costs although disease progression of RA has been postponed and slowed with biologics. Higher direct costs were consistently observed when the entire or a high proportion of the population were on biologic treatments ($9,618-$26,964 versus $401-$9,493). Indirect costs continue to contribute a considerable proportion to total costs in the biologic era, with work disability accounting for the majority of costs. However, the strength of the current evidence is not sufficient to conclude that biologics live up to their promise that expensive drug costs could easily be recovered. Thus, economic cost analyses that exclude or only partially include indirect costs will underestimate the full economic impact of RA.

In the value-based pricing system, criteria such as those for severe diseases, addressing unmet needs, innovative technologies, and having wider societal benefits are well supported by the general public.(361) A COI study provides a clear understanding on where the costs are incurred and what cost savings are occurring as a consequence. However, owing to disparities in costing methodologies, perspectives, and healthcare settings across studies, even if they were undertaken in the same country, it is difficult to draw a meaningful chronological trajectory to examine the change in landscape. Ideally, future COI studies of RA ought to include both direct costs (including drug costs, hospitalisation, and outpatient attendance) and indirect costs (including costs associated with absenteeism, presenteeism and work disability). Furthermore, the inclusion and reporting of sensitivity analyses is vital for readers to understand the uncertainty around the COI estimates and the robustness of the conclusions that studies reach.(14) Sensitivity analyses can also be used to explore alternative methodological approaches that may lead to differences in results, such as FCA and HCA.

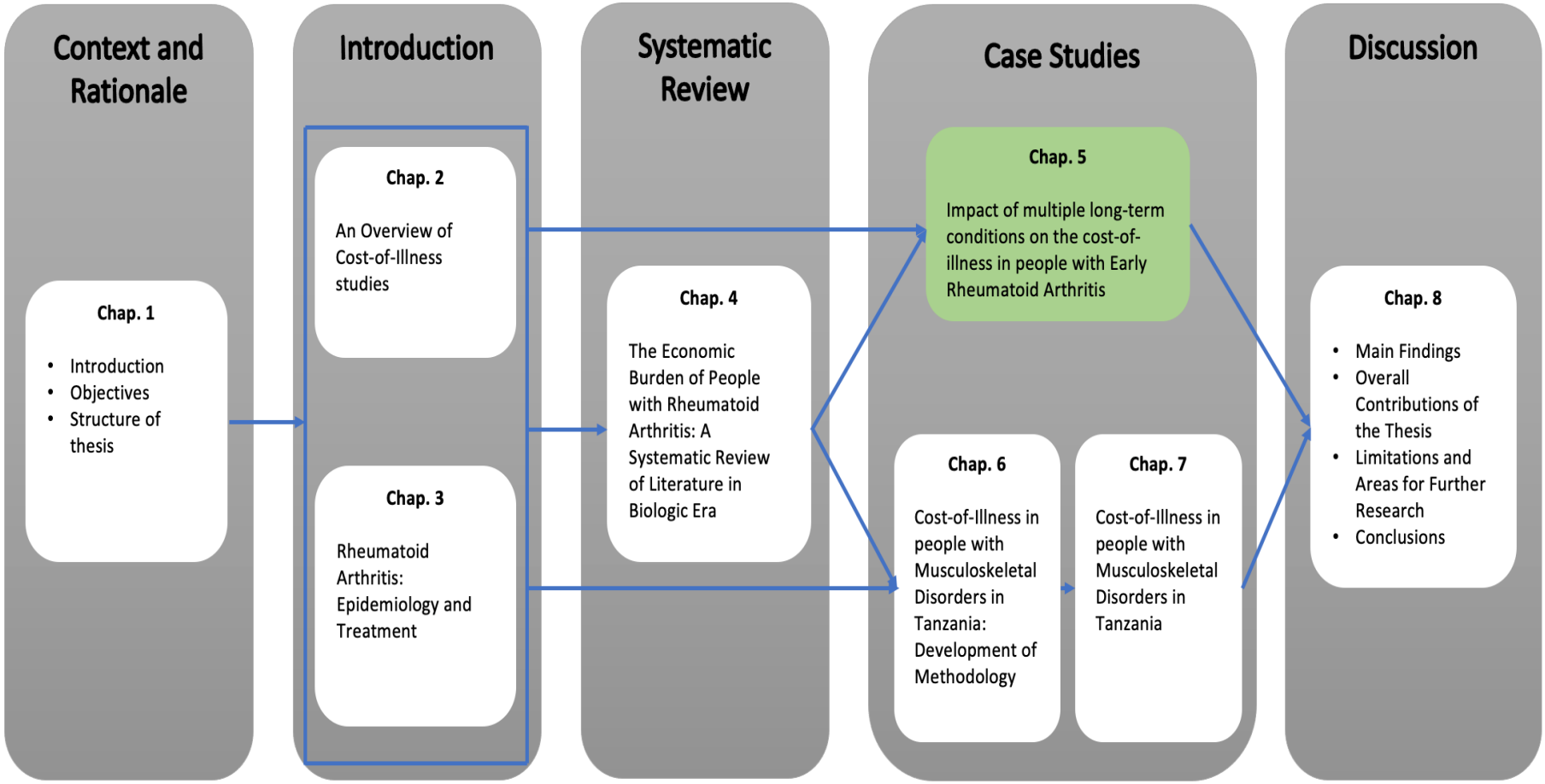
There are several limitations in this study. First, included studies were heterogeneous in terms of study design, costing approaches, or sample size, resulting in a high degree of uncertainty and large variation in cost estimates. There are additional methodological challenges which, together with the countries where the studies were performed, lead to variation in findings across studies. However, the objective was to ensure a truly comprehensive overview of the literature on the economic burden of RA. Second, because total costs included various components that were not homogenous in all studies, and a breakdown of total costs into individual components was not reported in all studies, it is not appropriate to pool estimates from different countries or to perform formal quantitative analyses (meta-analysis). Therefore, data was assembled and analysed narratively and focused on the similarities and differences across these studies, and how these impact on the overall COI. Third, only published English-language studies were included; therefore, some non-English studies will have been omitted.

Although not reported in any of the included studies, the advent of cheaper biosimilars provides the potential for reducing pressure on healthcare budgets. So far, there has been no COI study exploring the economic impact of biosimilars in RA since the first biosimilars for infliximab and etanercept were approved in the US and Europe in 2016. It has been suggested that highly equivalent and lower cost biosimilars could reduce the pressure on healthcare budgets and compensate for inequalities in access to therapy potentially caused by economic differences between countries.(362) However, challenges remain regarding price, biologics switching in clinical practice, and post-marketing pharmacovigilance.(363) Hence, future studies should focus on the economic impact of informal care from patients' perspective, presenteeism, and the entry of biosimilars.

4.6 Chapter Summary

In this chapter, the findings suggest that drug costs comprised the main cost component of direct costs in the biologic era while the proportion of hospitalisation was decreasing over time. Nevertheless, indirect costs still contribute considerably to total costs, with work disability being the main cost component. Therefore, economic analyses without taking indirect costs into account or measuring properly will underestimate the full economic impact of RA.

This chapter serves as a foundation for the two case studies of this thesis. It highlights two major methodological challenges: comparability and reliability. Studies use different definitions for COI with varying methodological approaches. In particular for indirect costs, the choice of cost methodology can significantly influence the magnitude of estimates, yet it is greatly driven by data availability, which varies from setting to setting. Also, current evidence shows a lack of consistency in taking into account indirect costs, resulting in underestimating COI in RA. The next chapter will present the first empirical study, developing a COI study using a RA inception cohort linked with routinely collected health data.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CHAPTER 5. IMPACT OF MUTILPLE LONG-TERM CONDITIONS ON THE COST-OF-ILLNESS IN PEOPLE WITH EARLY RHEUMATOID ARTHRITIS

5.1 Introduction

As demonstrated in Chapter 4, numerous cost-of-illness (COI) studies in rheumatoid arthritis (RA) exist but there is a paucity/absence of studies that have been conducted in the UK in the biologic era, or that have studied early RA, particularly in an inception cohort. Previous studies use different definitions for COI with varying methodological approaches. The choice of COI methodology can significantly influence the magnitude of estimates, yet it is greatly driven by data availability, which varies from setting to setting. One striking feature is the lack of consistency in taking into account indirect costs, and even when the studies do that, the approach to estimating COI varies. For studies where indirect costs dominated, it was observed that work disability measured by disability pension was taken into account in these studies.(324-326, 336, 344) In contrast, when indirect costs mainly consisted of sickness absence, a lower percentage of indirect costs was observed.(106, 333, 345, 356-358) As a result, annualised estimates of total direct and indirect costs range from $2,408 to $83,845 for a RA patient, and the proportion of indirect costs varies from 3.3% to 85.5% across studies.(62) For a chronic disease like RA, that predominantly occurs in women, the approaches to collecting, measuring, and valuing indirect costs are of great critical importance.

COI studies can be described as prevalence-based or incidence-based approaches based on the way in which the epidemiological data are used as introduced in Chapter 2. The former approach estimates the economic burden of a condition over a specific period, while the latter approach estimates the lifetime costs of a condition from its onset until its disappearance.(82) With the nature of long-lasting conditions such as RA that require considerably lengthy follow-up periods, the prevalence-based approach is more practicable

to measure. Indeed, according to the systematic review for COI studies in the previous chapter, only 5 out of the 72 included studies used the incidence-based approach. However, the predefined follow-up periods were not a lifetime in those incidence-based studies. Therefore, a prevalence-based approach will be used to develop a COI study in this chapter. Furthermore, to address the second Objective defined in Chapter 1, measurement and valuation of indirect costs will be explored by using available data and external information to discuss the advantages and limitations of methodologies in estimating COI and outline in which decision contexts insights from them might be useful.

As outlined in Chapter 1 and Chapter 3, interest in LTC and MLTCs (multiple LTCs) has been growing rapidly over the past two decades.(19-23) Traditionally, coexisting LTC or comorbidity has been defined as the "existence or occurrence of any additional entity during the clinical course of a patient who has the index disease under study".(24) In contrast, MLTCs has been defined as the coexistence of two or more LTCs in the same individual.(213) The accumulation of LTCs within an individual is associated with worse outcomes than having no other chronic conditions or a single condition.(25) MLTCs is now an established priority for both research (31) and clinical practice (32, 33) owing to the high prevalence of coexisting diseases among patients, particularly with ageing populations.

As introduced in Chapter 3 (Section 3.3.1), LTCs such as cardiovascular diseases,(133) infections,(217, 364) gastrointestinal diseases,(365, 366) malignancies,(367) osteoporosis and depression (303) are sub-optimally prevented, screened for and managed In people with RA.(294) Coexisting conditions in RA are associated with worse health and quality of life outcomes (216-219) and have a significant negative impact on functional ability, independent of disease activity.(220-222) In the context of an ageing population and the life-long nature of RA, the management of MLTCs is particularly relevant in order to

provide the best possible outcomes and to minimise unintended complications and costs.(23, 223) To date, existing studies have focused on the added economic burden associated with specific LTCs (368, 369) or groups of selected LTCs in established RA.(370-372) There is agreement that RA patients with comorbid conditions incur higher healthcare costs and a higher risk of work disability.(373) However, little is known about the impact of MLTCs on costs in early RA.

5.1.1 Research Questions

This chapter aimed to develop a COI in RA in the UK by using the an inception cohort linked to routinely collected health data. Since the retrospective data analysis has been the most widely used approach as identified in the systematic review in Chapter 4, this chapter discussed the methodological challenges by using this approach. In addition, due to the shift of focus on improving clinical outcomes in how we approach chronic diseases in medical research, it is pertinent that we also think about how this impacts the way we look at COI. This case study also described and quantified the impact of MLTCs on the COI, including direct and indirect costs for people with early RA. Therefore, there are two research questions for this chapter:

1) What are the methodological challenges in estimating the COI in RA using an inception cohort linked to routinely collected health data?
2) What is the COI in people with RA in Scotland and how do coexisting long-term conditions impact on the COI in people with early RA?

5.2 Methods

5.2.1 SERA Study

The Scottish Early Rheumatoid Arthritis (SERA) study (374-378) is a national multicentre, prospective inception cohort of people with newly diagnosed RA or undifferentiated

arthritis. Participants were recruited from rheumatology departments in 20 hospitals across Scotland between September 2011 and April 2015.(375) Participants with a new clinical diagnosis of RA or UA, who had at least one swollen joint, were invited to participate. RA was clinically diagnosed by a rheumatologist and the participants selected additionally met the 2010 ACR/EULAR RA classification criteria (379) at their baseline visit. Data were collected at baseline, then six-monthly intervals until year two and then annually thereafter until year five. Information on demographic characteristics, employment status, imaging and laboratory examinations were obtained during face-to-face study visits with research nurses from the participants. SERA was approved by the West of Scotland Research Ethics Committee 4 (reference 10/S0704/20) and all participants gave written informed consent.

Measure of Functional Disability

Functional disability was measured by the Health Assessment Questionnaire - Disability Index (HAQ -DI) in SERA, which includes eight categories, reviewing a total of 20 specific functions evaluate patient difficulty with activities of daily living over the past week. The eight functional categories cover dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and errands and chores. The total HAQ-DI score is between 0-3.0, in 0.125 increments. Increasing scores indicate worse functioning, with 0 indicating no functional impairment, 1 for some difficulty, 2 for much difficulty and 3 indicating complete impairment.(380)

Measure of Health-Related Quality of Life (HRQoL)

In chronic diseases like RA, HRQoL is the main outcome associated with physical function, pain and global health. It reflects patients' overall wellbeing, incorporating a multidimensional patient-centred concept. There is also evidence that an increasing number of comorbidities leads to a decrease in HRQoL.(224) During the face-to-face

interviews by research nurses, HRQoL was measured using the generic preference-based instrument (EuroQol-5d (EQ5D), 3-level version).(381)

5.2.2 Linked Health Data

SERA participants were also asked to consent to the linkage with their National Health Service (NHS) records for research purposes by the electronic Data Research and Innovation Service (eDRIS) team (part of Public Health Scotland). Where specific consent was not given, the linkage did not take place. As the NHS in Scotland provides universal coverage, the linkage allows for the creation of a comprehensive data source relating to hospital admissions, community prescription encashment, cancer registry, and death. Multiple deprivation, measured by the Scottish Index of Multiple Deprivation (SIMD),(382) was also linked to SERA participants' records. The SIMD quintiles reflect multiple deprivation in Scotland for shaping policies aimed at addressing issues related to areas with high levels of deprivation, where the most and the least deprived areas are ranked from quintile 1 to 5.(382) Linked records were available from the start of recruitment (September 2011) to November 2019 for this analysis.

Prescription Information Service (PIS)

The PIS database covers all NHS prescriptions prescribed, dispensed and reimbursed within the community setting. PIS provides summary information on reimbursed medicines from 1993, and it also gives access to individual prescribing and dispensing data since 2009.(383) The inclusion of this unique identifier in PIS allows for accurate health data linkage at an individual level with well-coded national and local databases, enabling studies to be conducted across individuals and populations' entire lifespan. Another important aspect of the database is data indicating whether a prescription was prescribed and dispensed. While prescribing authorises the use of prescriptions, dispensing means the actual number of prescriptions dispensed. The quality of PIS data is guaranteed by an

electronic system, which has eliminated errors linked to manual data entry processes, and by several stages of record quality checking before and after they are submitted to PIS.(384)

In terms of coverage, the NHS in Scotland provides universal coverage; therefore, PIS is representative of all age, sex and socioeconomic groups and geographies, is free from any selection bias and allows for the detection of rare events. Prescriptions must be submitted for payment so that the dispenser can be reimbursed for the products supplied, providing a strong incentive to do so. Data, therefore, have a high level of completeness.(384)
The linkage of PIS for SERA study provides patient-specific identifier, prescribing and dispensing dates, and drug data. For each reimbursed prescription, individual variables including the approved name, product name, British National Formulary (BNF) code, formulation and strength are available. Quantity information is available as the total paid quantity as well as the daily doses.

Scottish Morbidity Record 01 (SMR01)

The SMR01 records contain all general acute admissions, categorised as inpatients or day cases, discharged from non-obstetric and non-psychiatric specialities. Patient-level records are submitted by hospitals and health boards to the Public Health Scotland (PHS). While inpatient admission implies a hospital stay overnight, day cases refer to a planned attendance to a speciality for clinical care. Generally, it does not require patients to stay in the hospital overnight. Upon completion of a hospital episode defined from the date of admission to the discharge date, and regardless of whether it is an inpatient or day case, an SMR01 record is generated.(385)

Each episode includes episode management details describing the date, reason, type of admission, and structures where patients were admitted from or transferred to. In

particular, the type of admission would indicate whether a patient was admitted as a planned or with an emergency admission. The details on admission/transfer would indicate the type of location, such as private residence, institution, same or different clinical specialty, from which an individual came from prior to hospital admission. The discharge type specifies whether discharge from an inpatient or day case episode was regular or resulted from self-discharge or death.(385) Further, for every episode, the diagnostic code is recorded using the International Classification of Diseases, Tenth Revision (ICD-10) developed in 1992 by the WHO and implemented in Scotland in 1996.

ICD-10 is an index of diseases and injuries used to compare conditions for epidemiological and health management purposes. Within the SMR01 context, ICD-10 codes are reported for the primary diagnosed condition followed by up to five additional diagnostic codes, which can describe comorbidities.(385, 386) While ICD-10 seems to be an accurate coding system, it is argued that the increase from 17,000 codes in the previous version ICD-9 to 141,000 codes may have introduced some unnecessary complexity.(387, 388) Details on health boards and geographical locations expressed as urban-rural classifications are also included.

Scottish Morbidity Record 06 (SMR06)

Scottish Morbidity Record 06 (SMR06) is a national database of all diagnoses of cancer. Cancer registration is the collection, maintenance and management of data on every new diagnosis of cancer occurring in a population. In Scotland, approximately 55,000 cancer registrations are made annually.(389) In this chapter, the SMR06 records were analysed to identify cancer patients in the sensitivity analysis.

5.2.3 Data Cleaning

Prior to the analyses, the prescription and morbidity records (PIS, SMR01 and SMR06) were checked for quality and consistency. Patients' prescribing and morbidity records prior to entering the SERA study were removed. Precisely, 1,971,928 and 33,848 records were removed from PIS and SMR01datasets, respectively. Further, duplicates were removed from SMR01 if the date of admission, date of discharge, name of speciality, and ICD code for the first diagnosis were the same when comparing two or more episodes for the same patient. For the PIS dataset, duplicates with the same prescribing date, BNF code and paid quantity among individuals were removed. Regarding the SMR06 dataset, records with the same date, ICD-10 codes among individuals were checked for duplicates. Following quality control, the final number of PIS and SMR01 records were 367,810 and 4,851 after removing from the 20,739 duplicates in PIS and 38 duplicates in SMR01, respectively (Figure 5.1). For the SMR06 records, there were no duplicates identified among the 1,318 records.

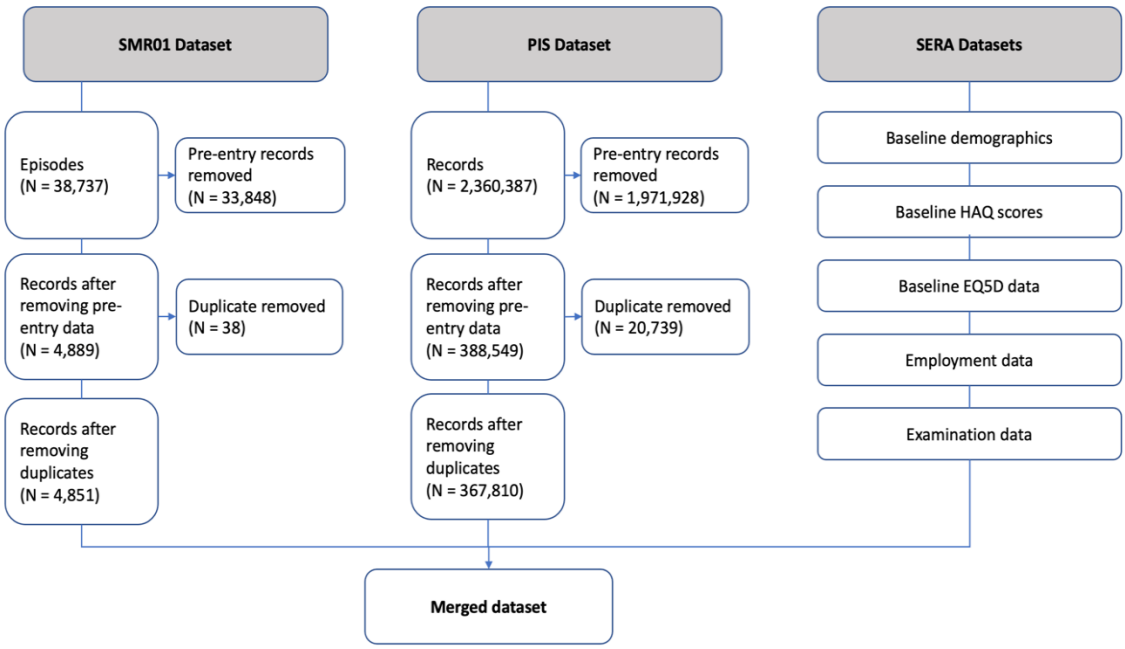


Figure 5.1 Data cleaning and preparation for the main analysis

Abbreviations: PIS = Prescription Information System, SERA = Scottish Early Rheumatoid Arthritis, SMR01 = Scottish Morbidity Records-general/acute inpatient daycase

5.2.4 Estimation of Cost-of-illness

The aim of COI studies is to itemise, value, and sum the costs associated of a disease to estimate its economic burden.(34) COI includes direct costs of treating the disease such as healthcare system costs for diagnosis, treatment and management of disease and the patients' own expenses, and indirect costs such as productivity loss resulting from time off employment.(390)

Direct Costs

Direct costs were defined as expenses from the perspective of NHS Scotland, using a bottom-up micro-costing approach. Costs for prescriptions in primary care, hospitalisations, imaging and laboratory examinations were included. Proxies for unavailable cost items (e.g. outpatient attendance, physiotherapy, occupational therapy, transportation etc.) were not used due to the difficulty obtaining data by LTC categories. As this case study was set up to investigate the impact of LTCs on the COI in RA, adding the same value to each LTC group will only increase the scale. Data sources for each cost component are provided in Table 5.1.

Prescriptions

Prescribing associated costs were not available in the PIS dataset, so that unit costs were obtained from the Scottish Drug Tariff (SDT) published by Public Health Scotland.(391) However, as BNF and Systematised Nomenclature Of Medicine (SNOMED) codes were used in PIS and SDT, respectively, an external dataset mapping BNF and SNOMED codes published by Business Service Authority NHS (392) was used to merge both PIS and SDT in order to assign unit costs. Firstly, the price per unit was obtained by dividing the item price by pack size. Secondly, the total number of items dispensed was obtained by multiplying the number of items dispensed. As the objective of this cost analysis is to

estimate total costs incurred by RA participants including coexisting conditions, all medications prescribed for the participants were included.

Hospitalisations

Mean unit costs per bed day and day case within specialities were obtained from Specialty Costs R040X and R042X in the PHS reports for the financial year 2019 to 2020.(393) Firstly, unit costs for each hospital admission episode were generated by linking the mean unit costs via speciality code and the identifier for day case and bed day. Secondly, costs for each hospital episode were obtained by multiplying the length of stay with the respective unit cost.

Examinations: Imaging and Laboratory

Mean unit costs for X-rays and blood tests were obtained from Hospital cost breakdown R120 and R130 in the PHS reports for the financial year 2019 to 2020.(393) Costs for examinations were obtained by applying relevant unit costs to resource use quantities in the SERA “BloodAndXray” dataset.

Table 5.1 Data sources for each cost component

Cost domain	Data source
Direct costs	
Prescription	PIS dataset PHS: Scottish Drug Tariff, NHSBSA: BNF SNOMED Mapping dataset
Hospitalisation	SMR01 dataset PHS: Specialty Costs R040X, R042X
Examinations	SERA: "BloodAndXray" dataset PHS: Specialty Costs R120, R130
Indirect costs	
Productivity loss, including paid and unpaid work	SERA: "Employ" dataset SMR01 dataset ONS: Weekly pay rate, gross (£) for all employee jobs in the United Kingdom at 2020 prices

Abbreviations: BNF = British National Formulary, NHSBSA = National Health Service Business Service Authority, ONS = Office for National Statistics, PHS = Public Health Scotland, PIS = Prescription Information System, SERA = Scottish Early Rheumatoid Arthritis, SMR01 = Scottish Morbidity Records-general/acute inpatient daycase, SNOMED = Systematised Nomenclature Of Medicine.

Indirect costs

The human capital approach was applied, reflecting lost productive potential.(39, 63, 148) Indirect costs were estimated from self-reported absenteeism of participants aged under 65 years, which was sickness absence due to health problems in the previous week. Given the data was only collected during nurse visits, participants who were hospitalised were also assumed to be absent from their work. The length of stay in hospital was therefore added to self-reported sickness absence for each participant and multiplied by age and sex-specific average weekly wages obtained from the Office for National Statistics (ONS, Table 5.2) to generate indirect costs.(394)

Table 5.2 Mean weekly pay rate, gross (£) for employee jobs in the United Kingdom at 2020 prices

Age group	Male	Female
18-21	274.5	221.9
22-29	526.4	442.6
30-39	702.5	519.0
40-49	814.0	529.1
50-59	772.6	494.4
Over 60	583.2	348.5

Source: Office for National Statistics (394)

In addition to paid work, the societal value of unpaid work was estimated by the opportunity cost approach for participants who were not in employment.(98, 395) In the opportunity cost approach, the value placed on lost unpaid work was determined by the age and sex-specific average weekly wages in Table 5.2.

5.2.5 LTC Grouping: Charlson Comorbidity Index

Coexisting LTCs result in increased healthcare cost and treatment interference in addition to excess mortality. Also, LTCs have a significant negative impact on quality of life, causing functional disability, independent of disease activity.(220-222) Comorbidity scores are a common tool used by researchers in epidemiological and health services research. The Charlson Comorbidity Index (CCI) is one of the most widely used comorbidity indices,(221, 396-398) and has been used in rheumatology.(221, 396) It is associated with outcomes such as inpatient mortality, length of hospital admission, readmission rate, functional disability, and healthcare utilisation.(399-401) The CCI was published in 1987 to predict 1-year mortality in a cohort of patients admitted to medical service and then validated in a cohort of breast cancer patients. It has 19 conditions (16 diseases, of which 3 are stratified according to severity) weighted differently based on their mortality association and then added to give the index score.(398) Although that was not its original intention, the CCI has been widely used to predict disability and functional status. It has

been used in rheumatology and has shown that comorbidity leads to increased disability in RA patients.(221, 396) Furthermore, the CCI has been shown to be a significant independent predictor of mortality in a population-based prevalence cohort with RA.(397)

Within the SMR01 context, ICD-10 codes are reported for the main diagnosed condition (primary diagnostic position) followed by up to five additional diagnostic codes, which can describe comorbidities.(385, 386) The CCI score was calculated using the R package *comorbidity* (402) to identify relevant ICD-10 codes in all hospital records throughout the follow-up period. Once a condition occurred, it was considered to be prevalent throughout the remainder of the follow-up. The number of LTCs was categorised into three distinct groups, including “RA alone”, “RA plus single LTC”, and “RA plus MLTCs (>1 LTCs)”.

5.2.6 Econometric Model

Following a prevalence-based approach to estimating the economic burden of RA over the follow-up period, two main methods have been widely used to estimate the financial burden of a disease, which are the global comprehensive approach and medicalised approach.(403) The former includes all the expenditures incurred by a population with a particular disease. From a methodological perspective, the comprehensive approach provides an upper bound for the estimation of COI. It provides an accurate picture of the overall expenditure of the population with a given disease. While the medicalised approach can be used to identify precise expenditures, it may also lead to underestimation or overestimation of the economic burden of a given disease; this may happen when cost estimation is not adequately adjusted for confounders highly correlated with the disease of interest.(403) Given the objective was also to quantify the impact of MLTCs on COI in RA patients, the global comprehensive approach was used to include all expenditures incurred by RA patients, adjusting for relevant confounders.

As discussed in Chapter 2, the regression-based approach is commonly used in the literature to take into account two important characteristics of the distribution of health care expenditure: the large number of subjects with zero expenditure and the heavily skewed distribution.(106, 184-188) The various models reported in the literature comprise two-part models designed to take zero expenditure into account. The first part models the individual's decision to access health care services, i.e., the probability of having health care expenditure different from zero. The second part determines the level of health care consumption in the subsample of individuals with health care expenditure different from zero. This two-part model is based on the hypothesis that the decision to access health care and the level of health care consumption are not correlated and that these two parts are independent.(404)

To analyse the data with an excessive number of zero values in hospitalisations, examinations and indirect costs, a two-part model was employed. In the first modelling part, a binary choice model was fit for the probability of observing a positive-versus-zero outcome. Furthermore, the level of incurred costs in the second modelling part was estimated using a generalised linear model (GLM). Because of the skewness of the cost data, the log-link function with a gamma distribution was chosen in the GLM, rendering the data symmetric to evaluate effects on COI associated with RA.(85, 403) Costs for prescriptions were estimated using a GLM model separately. Total costs were calculated by combining direct and indirect costs.

Econometric Model Covariates

Age

RA and associated LTCs are age-related conditions and may have an impact on overall costs expected to increase as the RA cohort ages. While costs for prescriptions and hospitalisations are expected to increase marginally with age, productivity loss due to work

loss is assumed to increases with age until retirement age when estimated by HCA. Participants' age was included as a categorical measure, where the youngest age group (under 45 years) served as the reference group.

Sex

RA is a disease that is more prevalent in women. It is assumed that costs differ between males and females, in particular those for productivity loss. In this econometric model, male was used as the reference category.

Functional Disability

The HAQ-DI score has been shown to be the strongest predictor of long-term outcomes in RA, including work disability and economic loss.(405, 406) It has been shown to be the most important predictor of mortality, compared with other patient measures, including radiographs, joint counts, and laboratory values.(405) Studies show that after an immediate rise in HAQ-DI at RA onset, mean HAQ-DI scores increase slowly over time (0.01–0.016 units per year) similar to the general population and are affected by treatment and comorbid conditions.(407-409) The HAQ-DI score at baseline was used in this model to adjust for patient's functional disability as a continuous variable.

HRQoL

In chronic diseases like RA, HRQoL is the primary outcome associated with physical functioning, pain, and mental health. It reflects patients' overall wellbeing, incorporating a multidimensional patient-centred concept. Previous studies have shown that an increasing number of morbidities leads to a decrease in HRQoL.(410) In this model, EQ5D responses at baseline were converted into utility values with UK tariffs by the R package *eq5d*.(411) The utility value at baseline entered the econometric model as a continuous variable.

Socioeconomic Status

Socioeconomic status (SES) can be one factor influencing health. There are multiple pathways through which SES affects health, including its impacts on individual health behaviours and lifestyles, exposures to environmental stressors and toxins, and access to health care.(412) In this econometric model, participants' SES was controlled for using SIMD quintiles.(382) The most deprived category (quintile 1) was used as a reference category for cost estimation, and any increase or decrease in cost estimates was compared against this category.

Follow-up years

As treatment-related costs may differ over the RA disease course, the number of years since entering the SERA study was included in the models that estimate direct costs, with the index year used as the reference group.

5.2.7 Sensitivity Analyses

I. Indirect Costs

One significant methodological challenge in this chapter is the data availability for measuring indirect costs. As described in Section 5.2.4, indirect costs were mainly measured using self-reported sickness absence and days spent in hospital. However, data on self-reported sickness absence in the previous week was only collected during nurse visits. Similar to many disease registries, the SERA study has limitations when it comes to maintaining follow-up visits beyond year 1. The number of nurse visits received over the study period can vary across participants. Hence, the first sensitivity analysis was carried out to assess the uncertainty around sickness absence in RA patients.

External information on estimated annual sick leave by gender from the TIRA2 cohort study was used in sensitivity analysis.(325) The TIRA2 study comprised 463 participants

recruited between 2006 and 2009 in Sweden, with comparable demographics (67% women with a mean age of 58 years) to RA participants in SERA. The number of days with sick leave was reported during all outpatient visits and hospital admissions using a health economic questionnaire. In this sensitivity analysis, the same age and gender-specific average weekly wages from the ONS (Table 5.2) were employed to generate indirect costs.

II. EULAR List of Comorbidities

As the CCI was not explicitly developed for RA, it may not capture LTCs frequently found in RA patients. Therefore, the six common comorbidities listed in the European Alliance of Associations for Rheumatology (EULAR) recommendations were chosen as an alternative multimorbidity grouping to investigate the impact of RA-specific comorbidities on the COI in RA. The list of comorbidities, including CVDs, gastrointestinal diseases, infections, depression, malignancy and osteoporosis, were highlighted for early screening and managing in RA patients.(294) These comorbidities are essential to consider because they are frequently observed in RA and impact health and quality of life outcomes.(216-219) Given multiple data sources were used and integrated to identify these comorbidities, the EULAR list was included as an alternative LTC grouping method rather than for direct comparison of the CCI.

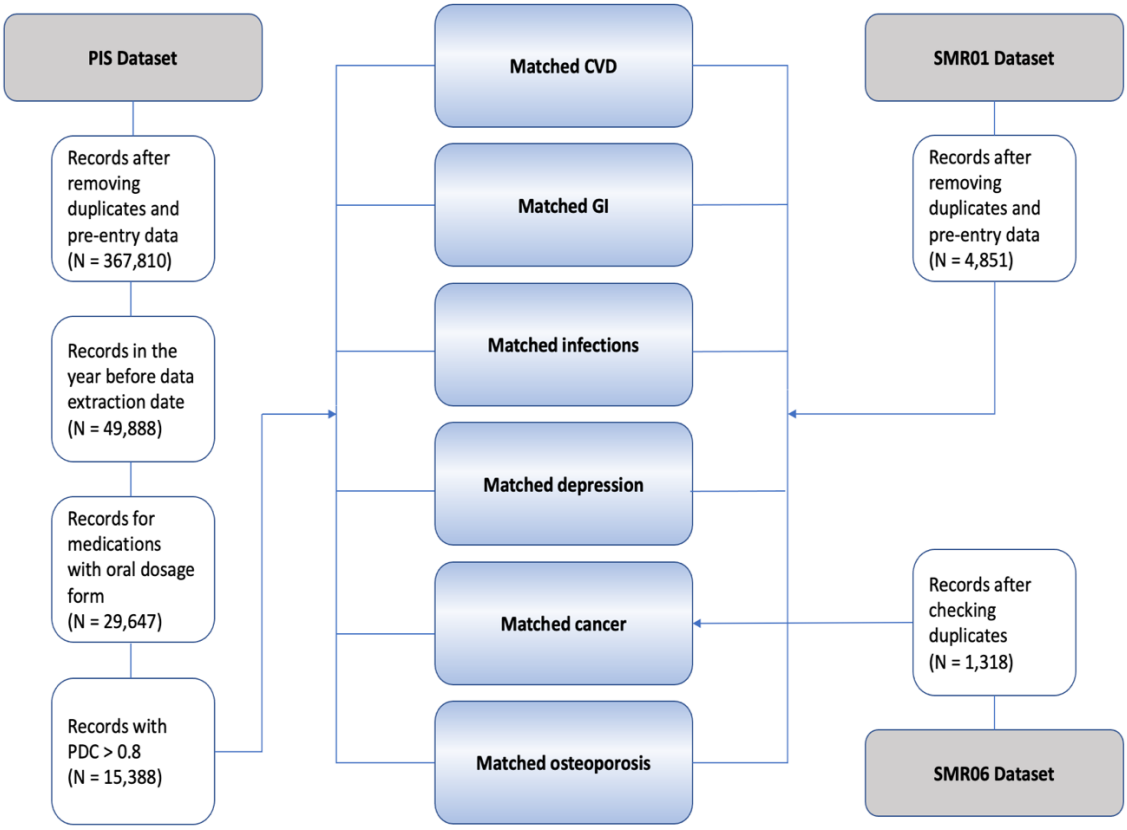


Figure 5.2 Data preparation for identifying EULAR list of comorbidities

Abbreviations: CVD = cardiovascular diseases, GI = Gastrointestinal diseases, PIS = Prescription Information System, SMR01 = Scottish Morbidity Records-general/acute inpatient daycase, SMR06 = Scottish Morbidity Records – cancer registry

The PIS, SMR01 and SMR06 datasets were used to identify RA-specific comorbidities (Figure 5.2). In the PIS dataset, the Proportion of Days Covered (PDC) approach was applied to identify these comorbidities via the BNF code of each prescription. PDC is comprehensively used in administrative claim data to assess medication adherence. It is calculated by using the number of follow-up days covered with medication divided by the total number of days in follow-up, where over 0.8 denotes 'good adherence'.(413-415) Patients with good adherence to a specific medication were assumed to have the associated health conditions. Firstly, duplicates and data before the entry date of SERA were removed. To assess associated costs of RA comorbidities that occur as a result of subsequent conditions arising from RA, the year before the data extraction date (31/10/2018 – 30/11/2019) was set as the index period. Secondly, the days covered for each prescription was calculated by the prescribed quantity divided by the maximum daily

quantity. Only medications taken with oral dosage forms, including tablet and capsule forms, were incorporated due to feasibility considerations. Accordingly, PDC was calculated by the sum of days covered divided by 365.25 (days) for each medication prescribed to individuals. Medications with a PDC over 0.8 were selected to further identify the six comorbidities of interest by the inclusion criteria listed in Table 5.3.

Table 5.3 Inclusion criteria for EULAR list of comorbidities

Disease of interest	Diagnostic and drug codes
Cardiovascular diseases	ICD-10: I00 – I99
	BNF: 0202, 0205, 0206, 0209, 0210, 0212
Gastrointestinal diseases	ICD-10: K20 – K95
	BNF: 01
Infections	ICD-10: A00 – A99, B00 – B99
	BNF: 05
Depression	ICD-10: F30 – F39
	BNF: 0403
Malignancy	ICD-10: C00 – C99, D00 – D49
	BNF: 08
	SMR06: any type of cancer
Osteoporosis	ICD-10: M80 – M85
	BNF: 0606, 090604, 090501

Abbreviations: BNF = British National Formulary, ICD: International Classification of Diseases.

For the SMR01 records, relevant ICD-10 codes relating to the EULAR list of comorbidities were identified using all diagnostic positions in any hospital admission during the follow-up period. In addition, the SMR06 data was analysed to determine cancer patients. Lastly, results from the PIS, SMR01 and SMR06 datasets were combined to identify the LTCs of interest.

5.3 Results

Of the 818 participants, 45 were recruited in 2011, followed by 339 in 2012, 270 in 2013, 151 in 2014 and 13 in 2015 as presented in Table 5.4. The sequential analysis on research nurse visit is presented in Figure 5.3. Overall, the SERA participants had 5.5 visits on average (range: 1-14, IQR: 4 – 7). Most visits occurred between 2012 and 2015. The sequential analysis shows a gradually decreasing gradient in nurse visits over the follow-up periods. Yet, there was a small number of patients returned in the subsequent years.

Table 5.4 Participants entry timeline

	2011	2012	2013	2014	2015
Number of patients	45	339	270	151	13
Cumulative sum	45	384	654	805	818

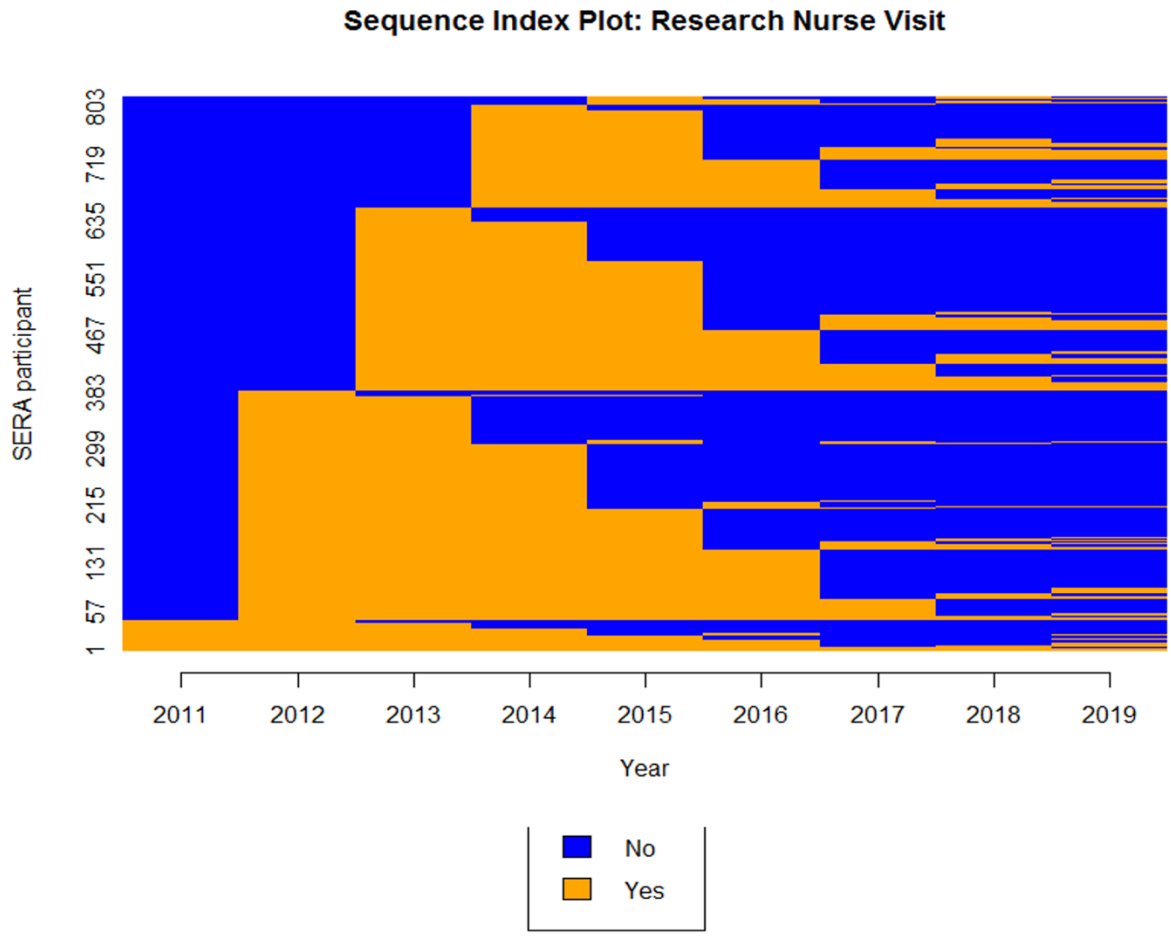


Figure 5.3 Sequence index plot on research nurse visit

5.3.1 Baseline demographics and clinical outcomes

The participants' demographic characteristics, stratified by LTC group, are shown in Table 5.5. Overall, the population included 66.3% women and 33.7% men. Mean (SD) age was 58.3 (13.7) years when recruited. During the follow-up period, the majority (68.8%) of the 818 participants with RA in SERA had no LTC, while 18% and 13.2% had a single LTC and MLTCs, respectively. Females accounted for 69.9% among the RA alone group; however, the proportion of females decreased with LTC category. The highest proportion of male participants (47.2%) was observed in patients with MLTCs. At baseline, individuals with RA plus MLTCs were older (65.5 vs 57.8 vs 54.6 years) than those with RA alone or with a single LTC.

Regarding socioeconomic deprivation measured by the SIMD quintiles, the composition of their living areas for participants with RA alone was evenly distributed across SIMD quintiles 1 to 4 (20.2 – 22.0%), except for a smaller proportion of participants in the most affluent areas (15.4%). Notably, more than a half of people with MLTCs lived in the most deprived areas (quintiles 1 and 2), where only 10.2% of them lived in the most affluent area.

As to clinical outcomes at baseline, the mean HAQ-DI score was1.21 (SD: 0.78) for RA alone participant, while the functional ability was worse among those with RA + MLTCs (1.41±0.84). Meanwhile, the mean EQ5D score slightly decreased from 0.53 (SD: 0.21) to 0.49 (SD: 0.24) with the level of LTC category.

Nearly 60% of the participants with RA alone remained working when recruited, including full-time and part-time employment, and self-employed. However, the proportion of paid and unpaid work decreased with the level of LTC category, while retirement was the opposite.

Regarding resource utilisation, individuals with MLTCs had more hospital admissions or day case attendances per person-year than those having a single LTC or with RA alone (2.24 vs 1.02 vs 0.39), as well as a longer average length of stay for each hospitalisation throughout the follow-up period.

Table 5.5 Baseline demographics and clinical outcomes by LTC group

	RA alone	RA + Single LTC	RA + MLTCs
Participants	563	147	108
Age (years)	56.4±13.4	63.3±12.6	67.6±9.9
Age groups (n)			
45 and younger	18.7% (120)	6.1% (9)	0% (0)
45 – 54	25.3% (149)	19.7% (29)	15.7% (17)
55 – 64	28.3% (153)	25.2% (37)	19.4% (21)
65 – 74	19.9% (107)	29.3% (43)	43.5% (47)
Over 75	7.8% (34)	19.7% (29)	21.3% (23)
Gender (n)			
Male	30.1% (172)	36.1% (53)	47.2% (51)
Female	69.9% (391)	63.9% (94)	52.8% (57)
SIMD (n)			
1 (most deprived)	22.0% (107)	18.4% (27)	26.9% (29)
2	22.0% (120)	26.5% (39)	25.9% (28)
3	20.5% (113)	17.0% (25)	13.0% (14)
4	20.2% (128)	19.0% (28)	24.1% (26)
5 (least deprived)	15.4% (94)	17.7% (26)	10.2% (11)
Missing	1.4% (1)	0% (2)	0.0% (0)
HAQ-DI score	1.21±0.78	1.31±0.79	1.41±0.84
EQ5D score	0.53±0.21	0.53±0.23	0.49±0.24
Employment status[#] (n)			
Paid work	59.3% (334)	39.5% (58)	26.9% (29)
Unpaid work	4.6% (26)	3.4% (5)	1.9% (2)
Retired	29.1% (164)	49.0% (72)	66.7% (72)
Unemployment	5.9% (33)	8.2% (12)	3.7% (4)
Student	1.1% (6)	0% (0)	0.9% (1)
Hospitalisation[§]			
Yearly admission/day case	0.39	1.02	2.24
Length of stay (days)	2.56±4.0	3.68±6.8	4.28±9.5

Data are presented as mean±SD. LTC: long-term condition; SIMD: Scottish Index of Multiple Deprivation. [#]: Paid work includes full-time and part-time employment and self-employed; unpaid work refers to those answered 'homemaker'. [§]: measured over the 6-year follow-up period

5.3.2 Annualised direct and indirect costs, by LTC group

Regression results for direct costs

As there were no zero costs, a two-part model was not required for estimating direct costs. Therefore, the estimation of direct costs was adopted by a GLM model. Regression results are shown in Table 5.6. Overall, there was no statistically significant difference between men and women. The coefficients indicated a gradual increment in the likelihood with advancing age. In contrast, participants living in the most deprived areas incurred the highest direct costs, followed by a gradual decrement across the SIMD quintiles. In terms of clinical outcomes, worse functionality was associated with high direct costs. Compared to the index year, direct costs in the subsequent years were higher, particularly pronounced in the fourth year. Lastly, individuals having single LTC and MLTCs were strongly associated with higher direct costs than RA alone.

Regression results for indirect costs

Regression results for the two-part model estimating indirect costs are presented in Table 5.7. There was no significant difference between age groups, while the female gender appeared to be associated with lower indirect costs in the second modelling part. Participants who lived in the SIMD quintile 3 and 4 were less likely to incur indirect costs. For the clinical outcomes, participants with worse functional ability and HRQoL were more likely to incur indirect costs, although only HAQ-DI score was associated with higher incurring costs. Furthermore, individuals with single LTC and MLTCs were more likely to incur indirect costs as well as associated with higher incurring costs than RA alone.

Table 5.6 Regression results for the CCI grouping: coefficients of the GLM model estimating direct costs

Covariates	Coefficient (95%CI)	Std. Err	p Value
Sex			
Male	Reference		
Female	-0.012 (-0.191, 0.158)	0.094	0.898
Age group			
< 45	Reference		
45 – 54	0.221 (-0.087, 0.528)	0.157	0.159
55 – 64	0.406 (0.113, 0.698)	0.149	<0.01
65 – 75	0.485 (0.186, 0.785)	0.153	<0.01
> 75	0.688 (0.345, 1.030)	0.175	<0.001
SIMD			
1 (most deprived)	Reference		
2	-0.644 (-0.908, -0.381)	0.134	<0.001
3	-0.627 (-0.904, -0.350)	0.141	<0.001
4	-0.572 (-0.837, -0.308)	0.135	<0.001
5 (least deprived)	-0.379 (-0.669, -0.088)	0.148	<0.05
Clinical outcomes			
HAQ-DI score	0.178 (0.030, 0.327)	0.076	<0.05
EQ5D score	-0.107 (-0.622, 0.408)	0.263	0.684
Follow-up period			
Index year	Reference		
2	0.415 (0.127, 0.703)	0.147	<0.01
3	0.552 (0.262, 0.843)	0.148	<0.001
4	0.706 (0.414, 0.999)	0.149	<0.001
5	0.344 (0.049, 0.640)	0.151	<0.01
6	0.517 (0.218, 0.816)	0.153	<0.001
LTC group (using the CCI grouping)			
RA alone	Reference		
RA + Single LTC	0.867 (0.633, 1.110)	0.119	<0.001
RA + MLTCs	1.576 (1.300, 1.851)	0.141	<0.001

Abbreviations: CCI = Charlson Comorbidity Index, EQ5D= EuroQol- 5 Dimension , GLM= generalised linear model, HAQ-DI= Health Assessment Questionnaire-Disability Index, LTC= long-term conditions, MLTCs= multiple long-term conditions, RA= rheumatoid arthritis, SIMD: Scottish Index of Multiple Deprivation

Table 5.7 Regression results for the CCI grouping: coefficients of the two-part model estimating indirect costs

Covariates	1st modelling part (probability of incurring costs)			2nd modelling part (conditional on incurring costs)		
	Coefficient (95%CI)	Std. Err	p value	Coefficient (95%CI)	Std. Err	p value
Age group						
< 45	Reference			Reference		
45 – 55	-0.040 (-0.325, 0.255)	0.148	0.812	0.073 (-0.133, 0.279)	0.105	0.487
55 – 65	-0.095 (-0.371, 0.181)	0.140	0.501	0.162 (-0.033, 0.357)	0.100	0.104
Sex						
Male	Reference			Reference		
Female	0.215 (-0.020, 0.450)	0.120	0.073	-0.394 (-0.559, -0.229)	0.084	<0.001
SIMD						
1 (most deprived)	Reference			Reference		
2	0.050 (-0.266, 0.366)	0.161	0.755	-0.052 (-0.250, 0.146)	0.101	0.606
3	-0.351 (-0.684, -0.019)	0.170	<0.05	0.004 (-0.241, 0.233)	0.121	0.975
4	-0.457 (-0.773, -0.142)	0.161	<0.01	-0.168 (-0.382, 0.046)	0.109	0.125
5 (least deprived)	-0.330 (-0.693, 0.022)	0.180	0.066	-0.150 (-0.395, 0.095)	0.125	0.230
Clinical outcomes						
HAQ-DI score	0.640 (0.258, 0.627)	0.094	<0.001	0.156 (0.033, 0.279)	0.063	<0.05
EQ5D score	-2.094 (-2.051, -0.795)	0.320	<0.001	-0.171 (-0.589, 0.248)	0.214	0.425
LTC group						
RA alone	Reference			Reference		
RA + Single LTC	0.800 (0.482, 1.118)	0.162	<0.001	0.326 (0.140, 0.512)	0.095	<0.001
RA + MLTCs	0.856 (0.427, 1.285)	0.219	<0.001	0.617 (0.379, 0.854)	0.121	<0.001

Abbreviations: CCI = Charlson Comorbidity Index, EQ5D= EuroQol- 5 Dimension, HAQ-DI= Health Assessment Questionnaire-Disability Index, LTC= long-term conditions, MLTCs= multiple long-term conditions, RA= rheumatoid arthritis, SIMD: Scottish Index of Multiple Deprivation

Estimated cost-of-illness

Annualised direct costs for all RA participants were estimated to be £1,636 (95%CI 1,262-2,121). When combing costs for prescriptions, hospitalisations and examinations, average annualised direct costs incurred by people with MLTCs (£6,164) were 2.1 times higher than for those having a single LTC (£2,887), and 5.8 times higher than in people with RA alone (Table 5.8). Similarly, annualised indirect costs increased with LTC category. People with RA plus MLTCs incurred average annualised indirect costs 3.1 times higher (£842; 95%CI: 377-1,521) than people with RA alone (£271; 95%CI: 98-517) and costs were 1.6 times higher than those for people with RA plus a single LTC.

Annualised total costs for people with RA were calculated by combining direct and indirect costs and stratifying by LTC group. Total costs were highest for those with MLTCs, with direct costs accounting for 88.0%. For people with a single LTC and RA alone, 84.5% and 79.8% of total costs were attributable to direct costs, respectively.

Table 5.8 Annualised costs per person during the follow-up period

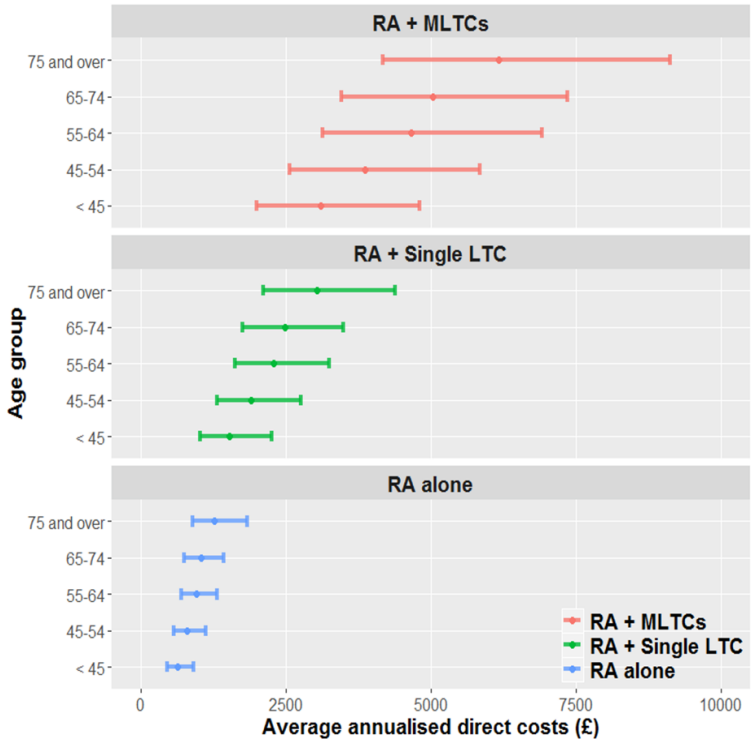
			LTC group £ (95%CI)			
Cost components	RA alone	%	RA + Single LTC	%	RA + MLTCs	%
Direct costs[#]	**1,071**	**79.8**	**2,887**	**84.5**	**6,164**	**88.0**
Prescriptions	144 (127-163)		193 (167-222)		225 (190-267)	
Hospitalisations	886 (223-2,140)		2,656 (837-5,817)		5,902 (2,110-11,282)	
Examinations	41 (9-74)		38 (7-76)		37 (7-75)	
Indirect costs	**271 (98-517)**	**20.2**	**530 (273-854)**	**15.5**	**842 (377-1,521)**	**12.0**
Total costs[*]	**1,342**		**3,417**		**7,006**	

[#] Direct costs were calculated by combining costs for prescriptin, hospitalisation and examninations. and stratifying by LTC group

[*] Total costs were calculated by combining direct and indirect costs and stratifying by LTC group

5.3.3 Costs by age and LTC group

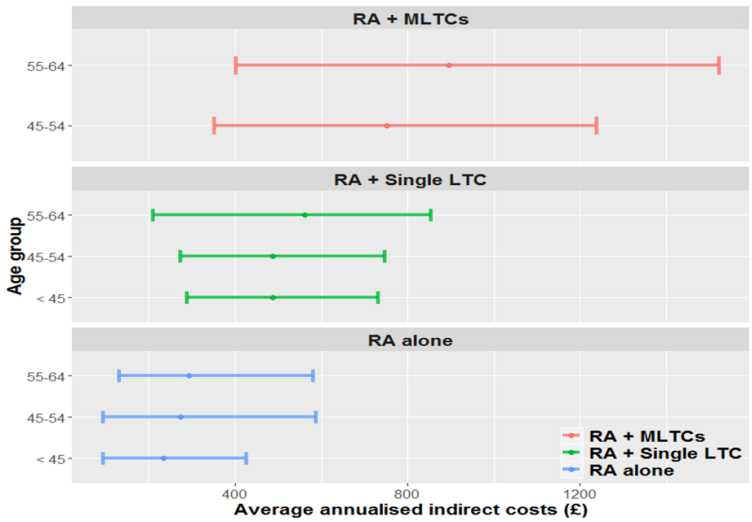
Annualised direct and indirect costs across age groups and LTC categories are shown in Figures 5.4A and 5.4B, respectively. Increasing LTC category was associated with increased direct mean costs for all age groups. While the 95% confidence intervals of direct costs overlapped for age groups within LTC categories, the age effect seemed to be more pronounced for categories of RA+Single LTC and RA+MLTCs compared with RA alone. For indirect costs, Figure 5.4B shows that there was no clear association with age in any LTC category. Accordingly, the proportion of direct costs gradually increased with age within each LTC category.



Mean (£, 95%CI)	% #
6,168 (4,172-9,119)	NA
5,039 (3,450-7,358)	NA
4,653 (3,129-6,918)	83.7
3,867 (2,560-5,841)	83.7
3,031 (2,003-4,802)	NA*
3,035 (2,104-4,377)	NA
2,479 (1,761-3,491)	NA
2,289 (1,618-3,240)	80.3
1,903 (1,313-2,758)	79.7
1,526 (1,032-2,2257)	75.8
1,276 (890-1,828)	NA
1,042 (756-1,437)	NA
962 (701-1,320)	76.7
800 (574-1,115)	74.6
641 (454-907)	73.4

The proportion of direct costs in total (direct and indirect) costs for those aged under 65 years within each age group; *: No observation under 45 years was found within RA+MLTCs.

Figure 5.4A Annualised direct costs by age and LTC category



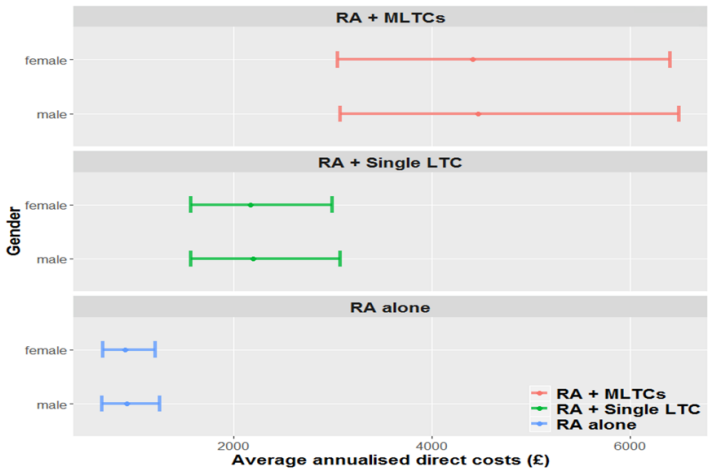
Mean (£, 95%CI)	% #
897 (403-1,521)	16.2
751 (351-1,239)	16.3
NA	NA*
562 (209-854)	19.7
487 (273-747)	20.3
488 (288-731)	24.2
293 (130-581)	23.3
272 (94-588)	25.4
232 (93-426)	26.6

The proportion of indirect costs in total (direct and indirect) costs for those aged under 65 years within each age group; * No observation under 45 years was found within RA+MLTCs.

Figure 5.4B Annualised <u>indirect</u> costs by age and LTC category

5.3.4 Costs by gender and LTC group

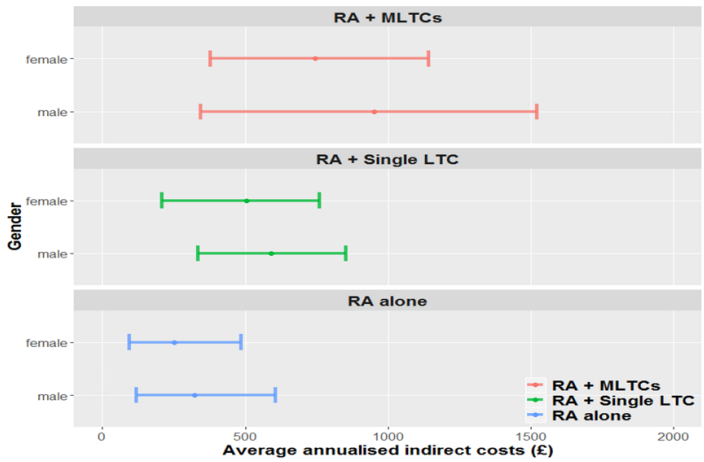
Figures 5.5A and 5.5B show annualised direct and indirect costs, respectively, by gender. Direct costs were comparable between men and women. However, indirect costs incurred by men were higher than those for women, regardless of LTC category.



Mean (£, 95%CI)	% #
4,118 (3,049-6,400)	84.7
4,471 (3,080-6,492)	82.5
2,174 (1,577-2,997)	81.1
2,200 (1,573-3,077)	78.8
914 (687-1,216)	78.2
925 (680-1,257)	74.2

The proportion of direct costs in total (direct and indirect) costs within each gender group.

Figure 5.5A Annualised <u>direct</u> costs per person by gender and LTC category



Mean (£, 95%CI)	% #
744 (378-1,144)	15.3
951 (346-1,521)	17.5
505 (208-760)	18.9
591 (335-854)	21.2
253 (93-486)	21.8
321 (120-607)	25.8

The proportion of indirect costs in total (direct and indirect) costs within each gender group.

Figure 5.5B Annualised indirect costs per person by gender and LTC category

5.3.5 Sensitivity Analysis I - Indirect Costs

To assess the uncertainty in indirect costs by using SERA and the linked health data, average sickness absence of 34.5 days for women and 55.1 days for men was adopted from an external source described in 5.2.6. When using the external data on sickness absence, this showed that annualised total costs were £6,206 when combining direct and indirect costs, of which 73.6% were attributable to indirect costs

5.3.6 Sensitivity Analysis II - EULAR List of Comorbidities

The second sensitivity analysis evaluated the alternative multimorbidity groups by using prevalent comorbidities highlighted by the EULAR recommendations. As presented in Figure 5.6, 367 participants with comorbid CVDs, 393 with GI diseases, 106 with infections, 109 with depression, 159 with cancer and 104 with osteoporosis were determined from the intersection of prescription records, hospitalisation and cancer registry. Accordingly, 234 (28.6%) participants were RA alone and 199 (24.3%) had a single LTC, and 385 (47.1%) were categorised as RA plus MLTCs by using the alternative LTC grouping (Figure 5.7).

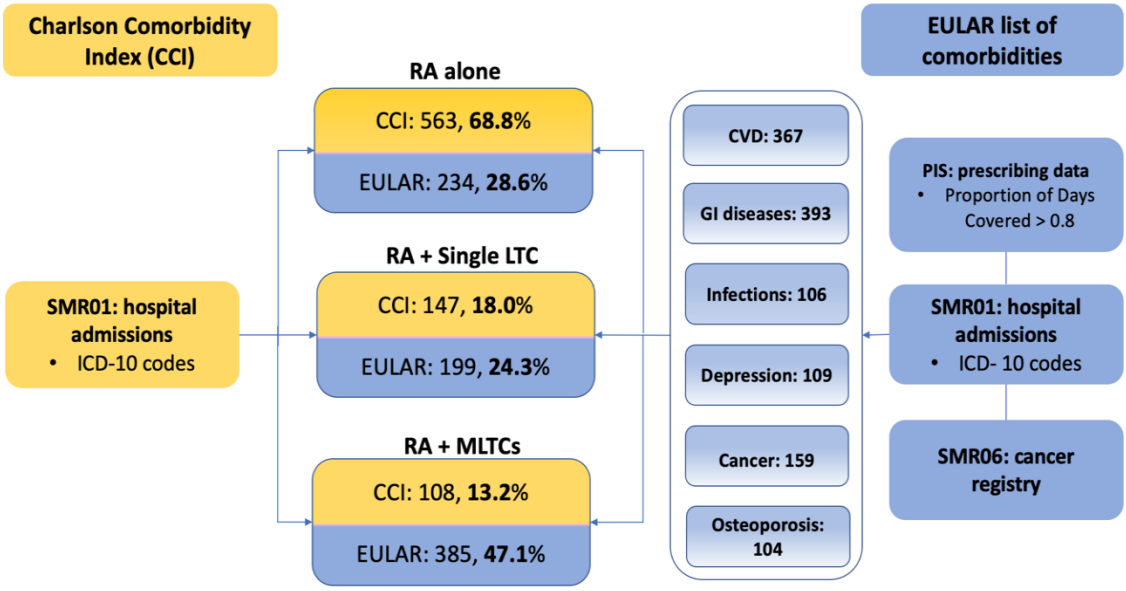


Figure 5.6 LTC groups by adopting the CCI and EULAR list of comorbidities

As shown in Table 5.9, annualised direct and indirect costs increased with LTC category by the EULAR list of comorbidities. Although the monetary values were substantially lower across all categories compared to the CCI grouping, it indicates that average annualised direct costs incurred by people with MLTCs were 2.9 and 6.1 times higher than RA plus a single LTC and RA alone, respectively. Similar with the CCI grouping, direct costs were primarily attributable to hospitalisation. In contrast, indirect costs incurred by RA plus MLTCs were 3.1 times higher than RA alone. Moreover, total costs attributable to direct costs were lower across LTC categories compared to the CCI.

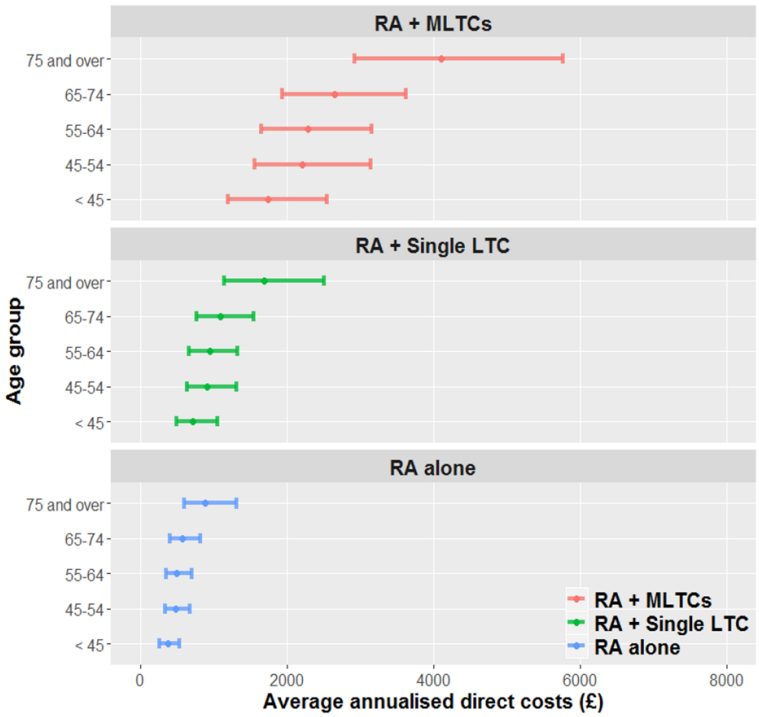
Table 5.9 Annualised costs per person during the follow-up period (EULAR)

Cost components	LTC group £ (95%CI) RA alone	%	RA + Single LTC	%	RA + MLTCs	%
Direct costs	**557**	**76.2**	**1,175**	**78.0**	**3,407**	**86.4**
Prescriptions	119 (103-137)		129 (112-149)		210 (185-238)	
Hospitalisations	396 (105-990)		1,008 (292-2,351)		3,157 (949-7,016)	
Examinations	42 (10-74)		38 (8-72)		40 (9-76)	
Indirect costs	**174 (68-378)**	**23.8**	**332 (150-639)**	**22.0**	**537 (266-946)**	**13.6**
Total costs*	**731**		**1,507**		**3,944**	

[#] Direct costs were calculated by combining costs for prescriptions, hospitalisations and examninations and stratified by LTC group

[*] Total costs were calculated by combining direct and indirect costs and stratified by LTC group

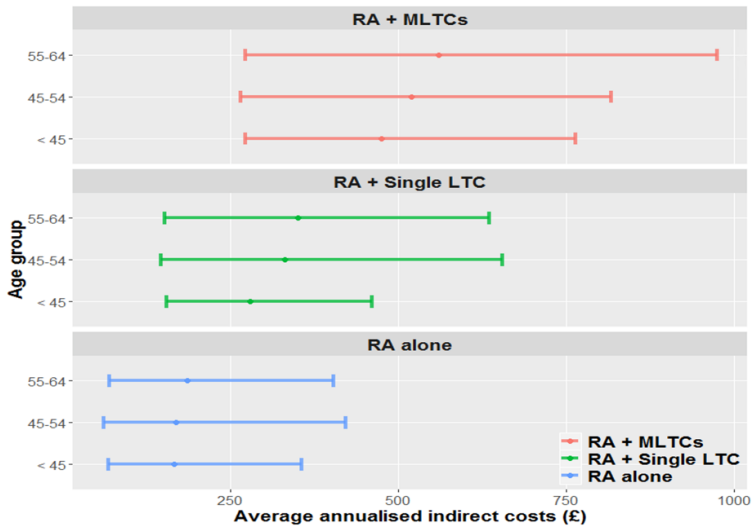
The annualised direct and indirect costs across age groups and gender using the alternative EULAR grouping approach are presented Figures 5.7 and 5.8. For direct costs, there also appeared to be an effect of increasing age associated with category of LTC, in particular for those aged over 75 years. Narrower 95% confidence intervals were found across age groups and LTC categories compared to the CCI grouping. Similarly, men incurred higher indirect costs than women, regardless of LTC category.



Mean (£, 95%CI)	% #
4,108 (2,926-5,767)	NA
2,644 (1,932-3,619)	NA
2,287 (1,656-3,159)	80.3
2,212 (1,559-3,139)	81.0
1,746 (1,201-2,539)	78.6
1,694 (1,148-2,500)	NA
1,090 (767-1,549)	NA
943 (669-1,329)	72.9
912 (635-1,309)	73.3
720 (490-1,059)	72.1
889 (601-1,316)	NA
572 (401-817)	NA
495 (350-700)	72.7
479 (337-680)	73.9
378 (265-540)	69.4

The proportion of direct costs in total (direct and indirect) costs for those aged under 65 years within each age group.

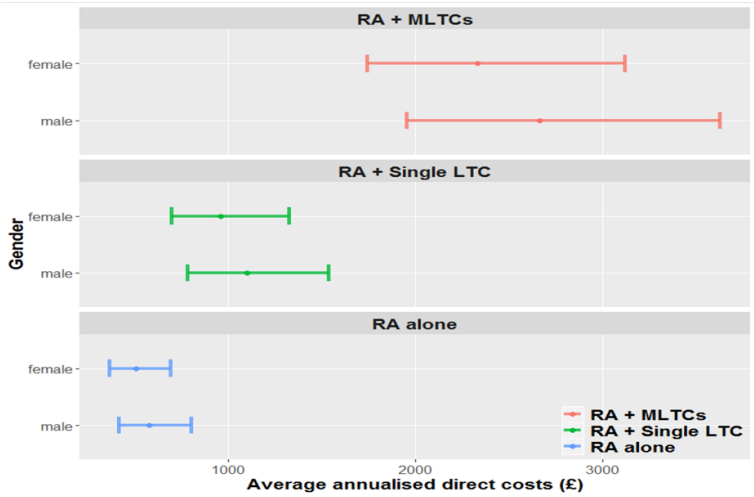
Figure 5.7A Annualised direct costs by age and LTC group (EULAR grouping)



Mean (£, 95%CI)	% #
560 (273-975)	19.7
520 (266-818)	19.0
475 (272-764)	21.4
351 (153-636)	27.1
331 (147-655)	26.7
279 (156-461)	27.9
186 (70-404)	27.3
169 (61-422)	26.1
167 (68-367)	30.6

The proportion of indirect costs in total (direct and indirect) costs for those aged under 65 years within each age group.

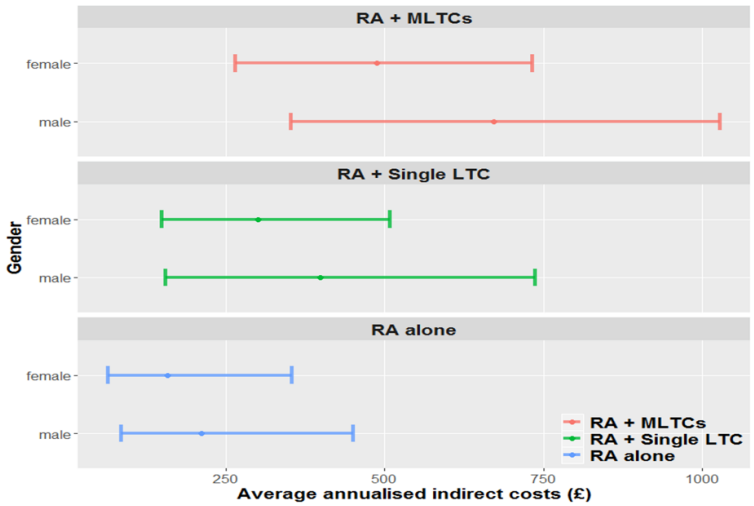
Figure 5.7B Annualised <u>indirect</u> costs by age and LTC group (EULAR grouping)



Mean (£, 95%CI)	% #
2,331 (1,742-3,120)	86.7
2,662 (1,954-3,627)	79.9
961 (697-1,326)	76.2
1,098 (783-1,538)	73.4
505 (368-692)	76.1
576 (414-802)	73.1

The proportion of direct costs in total (direct and indirect) costs within each gender group.

Figure 5.8A Annualised <u>direct</u> costs by gender and LTC group (EULAR grouping)



Mean (£, 95%CI)	% #
487 (265 -732)	17.3
671 (352-1,028)	20.1
300 (150-509)	23.8
398 (156-737)	26.6
159 (65-354)	23.9
212 (85-451)	26.9

The proportion of indirect costs in total (direct and indirect) costs within each gender group.

Figure 5.8B Annualised <u>indirect</u> costs by gender and LTC group (EULAR grouping)

5.4 Discussion

In this study, the economic impact on the cost-of-illness in people in Scotland with newly diagnosed RA was quantified stratifying by LTC category. The findings show that total annualised direct and indirect costs increased with the number of LTCs in addition to RA. Annualised direct costs incurred by people with early RA plus MLTCs were twice as high than for those having a single LTC and 4.8 times higher than in people with RA alone, respectively. People with RA plus MLTCs incurred average annualised indirect costs 3.1 times higher than people with RA alone and costs were 1.6 times higher than those for people with RA plus a single LTC. The relative proportion of direct costs increases with the number of LTCs, ranging from 77.2% to 84.1%. In addition to increased costs with LTC, the costs also generally increased with age and were higher for men regardless of the number of LTC categories.

The average annualised total costs in this study (direct costs: £1,636 95%CI 1,262-2,121; indirect costs: £362 95%CI 123-728) were lower than those reported in other recent studies, ranging from £2,987 to £3,742 for people with established RA.(416-418) Apart from different countries and health systems, one reason for the discrepancy may be due to the data availability for all cost items. Moreover, this study focussed on a population with early RA. For direct costs, appointments at general practice, outpatient clinics, physiotherapy and occupational therapy could not be estimated because of a lack of data. Secondly, prescription costs were only available from primary care, which will include most prescriptions, including conventional synthetic disease-modifying antirheumatic drugs (DMARDs), but not biologic therapies as information on medication prescribed in the hospital setting was unavailable. In line with national guidelines and standard clinical practice, people with RA have to fail at least two conventional synthetic DMARDs before starting a biologic DMARDs. As SERA is an inception cohort, all participants started on

conventional DMARDs (375) prescribed in primary care. Only 8% of the SERA participants were receiving biologic after a mean follow-up period of 18 months.(419)

For studies investigating the added economic burden of selected LTCs in RA, the approaches to categorising LTC category vary. A Thai study assessed the difference in direct costs between the presence and absence of LTCs,(372) while other studies have been more granular in their categories, e.g. 1 to 25 LTCs; the number of LTCs categorised into 0/1-2/3-4/≥5 groups.(370, 371) However, these studies were all limited to direct medical costs in established RA. This study evaluated the impact of MLTCs on both direct and indirect costs in people with early RA. Compared to indirect costs, direct costs increased more substantially with the LTC category. While the 95% confidence intervals of direct costs overlapped for age groups within LTC categories, the age effect seemed to be more pronounced for categories of RA+Single LTC and RA+MLTCs compared with RA alone. In addition to increased costs with LTC, the age effect seemed to be more pronounced for categories of RA+Single LTC and RA+MLTCs compared with RA alone, while there was no clear increase or association with age for indirect costs. As a result, the proportion of direct costs increased with age within each LTC category. Nevertheless, wide confidence intervals were observed, in particular for those with MLTCs. This implies that the level of MLTCs (e.g. severity and number of LTCs) was very heterogeneous.

Notably, estimates of the economic burden of RA suggest that the indirect costs of RA are substantial compared with the direct costs and may exceed these depending on how they are modelled, as mentioned in Chapter 4. Indirect costs in the main analysis only accounted for 18.1% of total costs for all participants under 65 years. In contrast, 73.6 % of total costs were attributable to indirect costs when adopting external sources on sickness absence from TIRA2, whether paid or unpaid work. In this study, data on sickness absence was collected during nurse visits. Missing data on nurse vsits during the follow-up period

also resulted in the underestimation of indirect costs. The quality and accuracy of collecting absenteeism could be improved by linking to social security data, as done with Swedish register data.(145-147) However, presenteeism and unpaid work, for example household work or care work, would still rely on self-reported data. Ignoring the impact of unpaid work could lead to underestimating the true costs, particularly for the RA population. Although indirect costs could not be measured fully using SERA linked to routinely collected health data as no detailed health economic questionnaire was available, the findings give an indication of the relative impact of LTC and MLTCs in early RA. How LTCs were measured did not change these findings.

Using the CCI, 68.8% of study participants were categorised as only having RA, while 18% had a single LTC, and 13.2% had MLTCs. However, comorbidity rates reported in the literature were between 60% and 75%,(420-422) and on average people with RA have 1.6 additional conditions.(222, 423, 424) Generic comorbidity measures are easy to use and compare across disease areas, but some diseases might be underrepresented due to the focus of the CCI on hospitalisations only. In contrast, 47.1% of participants in SERA were identified to have MLTCs using the EULAR grouping in sensitivity analysis. This was followed by 24.3% of people having a single LTC and 28.6% only having RA. These proportions are more comparable with the existing literature and show the importance of being able to capture co-existing conditions tailored towards the index disease.

The excess costs across LTC categories and higher proportion of direct costs when using the CCI compared to EULAR grouping may indicate that participants with a single LTC or MLTCs were more ill, as the CCI was driven by hospitalisation data. However, a similarly increasing direct and indirect costs trend with the LTC category was consistent when using either CCI or the EULAR grouping. The six comorbidities highlighted in the EULAR recommendations can easily be used to give an estimate of MLTCs burden, and therefore

impact on costs and outcomes, and can also serve as a potential framework to consider for future studies when detailed data on all LTCs is not available.

A major strength of this study is the ability to link between routinely collected healthcare records and a representative RA inception cohort in Scotland to conduct analyses that neither data source alone could accommodate. More importantly, our findings show that the impact of LTC on the COI occurs early in the disease, when there may still be an opportunity to intervene and change this. On the other hand, the COI may be underestimated due to data availability on outpatient attendance and medication received in the hospital setting. Besides, only absenteeism was included in indirect costs and subject to nurse visits; other societal costs such as presenteeism or details on unpaid work were not included as these require a health economic questionnaire to collect. As real-world evidence has gained significant momentum over the past decade, this has become a widely adopted study design when conducting a COI study. Although the evolution of routinely collected electronic data within care services provides new opportunities for collecting data without burdening patients or caregivers, self-reported methods will still be required when a societal perspective is desirable for the intended analysis.(212) Moreover, there is still a need to improve the methods for collecting, measuring and valuing indirect costs. Again, this is especially the case for a COI study from a societal perspective. Other key limitations are primarily inherent to the nature of administrative data, such as missing records or incomplete data. There is also the potential for miscoding in the morbidity records and misclassification of LTCs. For example, BNF codes were used to identify LTCs in the EULAR grouping; thus, misclassification might have occurred in certain medications with multiple indications.

5.5 Conclusions

Among people with early RA, people with MLTCs incurred direct costs that were almost five times higher and indirect costs that were three times higher than in people with RA only. The findings provide additional support for the importance of aggressive screening and early intervention to prevent the progression of MLTCs in people with RA. Both RA and LTC-related outcomes should be considered in formulating evidence-based policies and guidelines for RA management. Future research is needed for developing a validated tool to assess MLTCs and further understand the economic impact beyond direct medical costs and which clusters of LTCs contribute most to costs, and the impact of strategies to prevent or minimise MLTCs in RA.

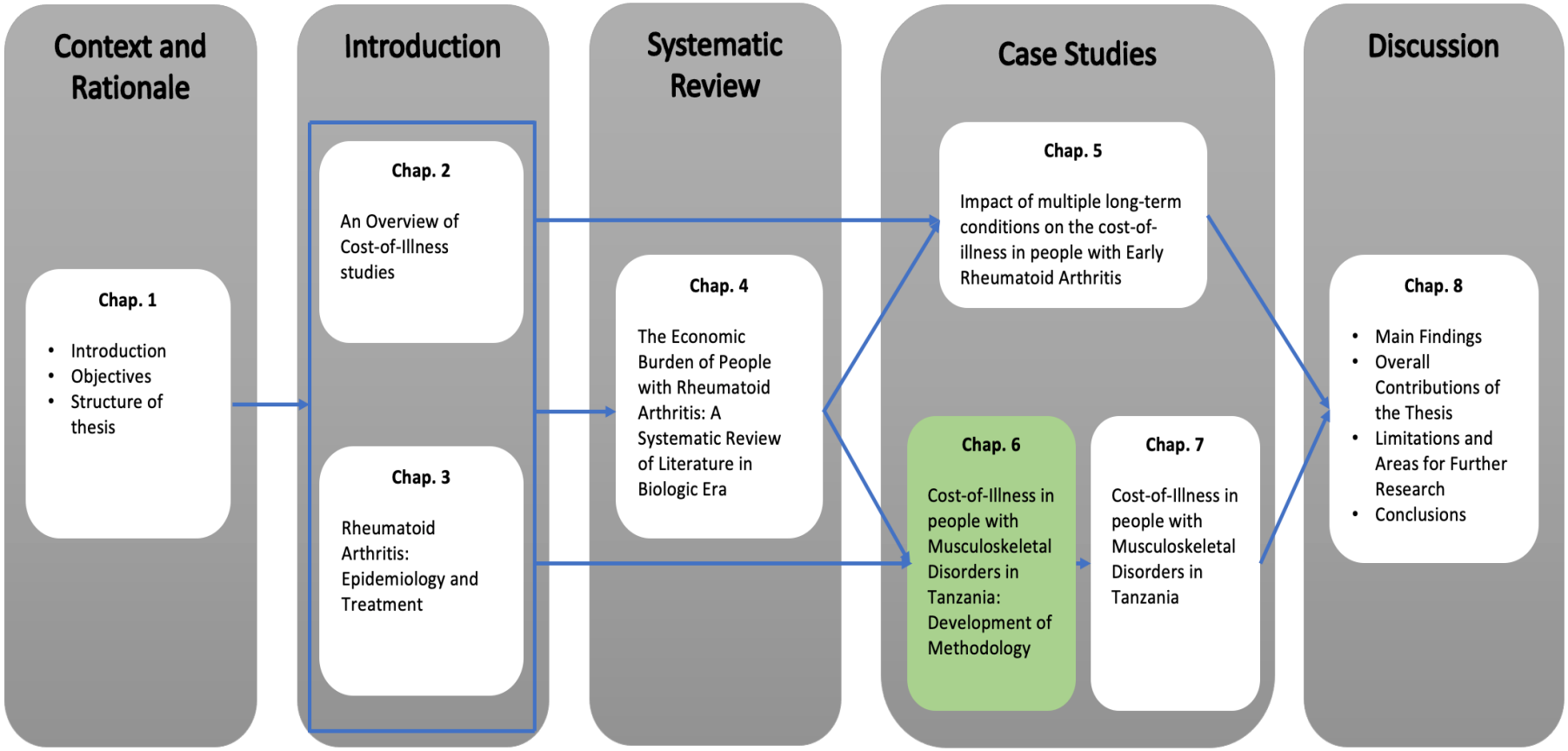
On the other hand, many LMICs are limited in their ability to offer appropriate care for chronic diseases at the primary care level because of socio-economic barriers, lack of comprehensive insurance coverage, uncoordinated care, and shortage of health personnel. More importantly, it is less likely to have a robust database for routinely collected health data in LMIC settings. As the focus of CCI is to identify relevant diagnosis from hospital records, using the CCI would be much more challenging to identify and measure comorbidities in many LMICs without sufficient data sources compared to the EULAR grouping. In contrast, brief, pragmatic tools to measure symptoms and problems across a range of relevant conditions (e.g., the EULAR list of comorbidities) may be more feasible to define and measure comorbidities in the LMICs.

5.6 Chapter Summary

As one of the empirical studies extended from Chapter 4, this chapter developed a COI study by leveraging the benefits of linking national cohort and administrative data together and discussing the methodological challenges. In addition to quantifying the COI in people with early RA in Scotland, it further investigated the impact of MLTCs on the COI in RA.

In this chapter, COI was estimated using a RA inception cohort linked with routinely collected health data. Indirect costs were estimated using information on self-reported sick leave in the previous week and length of inpatient stay from linked hospital data. Although the evolution of routinely collected electronic data has been beneficial for conducting a COI study, this study demonstrated the limitations on estimating indirect costs. For example, the quality and accuracy of collecting absenteeism could be improved by linking to social security data. However, there is still a need to improve the methods for collecting, measuring and valuing other components in indirect costs, such as presenteeism and unpaid work, when a societal perspective is desirable. Ideally, future disease registries or clinical trials should invest on incorporating measures of indirect costs at an early design stage.

The following two chapters will present the other case study, which was developed from a broader societal perspective in an LMIC setting, focusing specifically on the case of musculoskeletal disorders in Tanzania.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CHAPTER 6. COST-OF-ILLNESS IN PEOPLE WITH MUSCULOSKELETAL DISORDERS IN TANZANIA: DEVELOPMENT OF METHODOLOGY

6.1 Introduction

In Chapter 4 of this thesis, the systematic review for cost-of-illness (COI) studies in rheumatoid arthritis (RA) found that the majority of included studies were focused on high-income country (HIC) settings. Only 11 of the 72 studies were conducted in the upper or lower middle-income countries, including China, India, Mexico, Thailand, and Turkey,(345, 354, 357, 372, 425-431) and none was found in a low-income country (LIC) such as Africa. In the era of biologics, patients with RA in Africa are often seen at community health centres when seeking conventional healthcare and receive symptomatic treatment only, such as non-steroidal anti-inflammatory drugs (NSAIDs) or steroids for pain relief.(227)

Further, most of the 11 studies conducted in the upper or lower middle-income countries were conducted in hospital settings, with only six studies taking indirect costs into account by measuring work absenteeism.(345, 354, 357, 425-427) There is a distinct lack of COI studies in RA conducted in LMICs, particularly in Africa. This might be due to data availability, but also conceptual challenges in terms of what should be included in COIs in LMIC setting, as this will not be the same as in HICs. Importantly, indirect costs such as lost work productivity caused by musculoskeletal (MSK) disorders and arthritis are known to be greater than direct health care costs.(432-436) This is particularly pertinent to populations already experiencing significant poverty. Suspected high arthritis prevalence in countries like Tanzania exacerbates poverty by impacting ability to work and wider household/agricultural productivity as well as ability to fulfil community roles. Such high indirect costs and compounding impacts upon quality of life and depression are well

documented in developing countries but little evidence exists for Tanzania. This health and economic burden is under-reported in Sub Saharan Africa (SSA), including East Africa.

Chapter 2 discussed the theoretical background of COI studies and the conventional methodologies, however several anticipated differences in cost components and associated challenges need to be considered when conducting a COI study in LMICs. As noted by Briggs,(53) there are often differences in methodology adopted by researchers working in LMIC settings as compared to those working in HIC settings, resulting from different contexts. For direct costs, out-of-pocket (OOP) spending is increasingly recognised as an important barrier to accessing healthcare in LMICs, where a large proportion of health expenditure comes from OOP payments.(437) Also, travelling costs could be a financial barrier for people, resulting in buying medicine in pharmacies or seeking treatment using traditional medicine or healers. For estimating indirect costs in LMICs, challenges include that people may have multiple sources of income in LMICs,(437) informal employment is common, and income is often seasonal.(60, 61) Therefore, productivity loss would be difficult to measure only the workhour loss commonly used in developed countries.

In the first empirical study presented in Chapter 5, the COI study in people with RA in Scotland was developed by using routinely collected health records linked with inception cohort data. Although this approach can provide detailed information on health resource utilisation to measure direct costs, it also shows the limitation on capturing indirect costs. Only absenteeism was included and modelled for indirect costs; other societal costs such as presenteeism or details on unpaid work were not included as these require a health economic questionnaire to collect. In terms of context, many LMICs are limited in their ability to offer appropriate primary care for chronic diseases because of socio-economic barriers, lack of comprehensive insurance coverage, uncoordinated care, and shortage of

health personnel. Also, big data and patient registries are less likely to be available. Therefore, it would be much more challenging to estimate the COI by using routine data in an LMIC settings, where data is very sparse.

Given these challenges and gaps in methodology, this empirical study aimed to develop a COI study from a broader societal perspective in a LMIC setting. In the absence of routinely collected health data and the availability of screening tools for RA as it requires a blood test, a widening criterion of MSK disorders was adopted in the community survey. In the following sections, this chapter discusses the differences and challenges of the identification, measurement, and valuation of COI in LMICs and presents the development of methodology for the empirical study conducted in Tanzania in 2020/21.

6.1.1 Objectives

Learning from the first case study in Chapter 5, using linked routinely collected health data is convenient and relatively easy to conduct a COI study in RA. However, one of the major issues is data unavailable for all relevant cost components, particularly for indirect costs. Therefore, this chapter aimed to develop a COI study by using a dedicated primary data collection, incorporating measures of indirect costs at the early design stage.

This COI study was embedded as a sub study within a cross-sectional community survey in the Global Health Research Group (GHRG) – Arthritis study, funded by the National Institute for Health Research (NIHR).[1] This component of the empirical study aimed to estimate the COI in people living with MSK in Tanzania from a broader societal

[1] NIHR Global Health Research Group on estimating the prevalence, quality of life, economic and societal impact of arthritis in Tanzania: a mixed methods study at the University of Glasgow
Funding: National Institute for Health Research (NIHR) UK Government (Project 17/63/35)
Funding stream: Global Health Research Fund (ODA, DAC LIST LMIC) Project term 1st April 2018 - 31st March 2022, Budget £2,493,273

perspective. Due to additional considerations and justifications that need to be made for the LMIC context, it was divided into Chapter 6 and Chapter 7, separately presenting the development of methods and results. There are two research questions for this empirical study.

1) How has COI in RA been measured in LMICs and what are the methodological challenges?
2) What is the COI in people living with MSK in Tanzania?

The first research question is addressed in this chapter, discussing the methods for developing a COI study in a LMIC setting and pre-existing questionnaires for measuring COI, building on the global COI studies in RA identified from Chapter 4. A context-specific questionnaire was therefore developed by addressing the outlined methodological challenges. The second research question will be addressed in Chapter 7 by developing a COI study in Tanzania.

6.2 Economic burden of MSK in sub-Saharan Africa

For highly resource-constrained environments in sub-Saharan Africa (SSA), researchers have paid limited attention to the economic burden imposed by non-communicable diseases (NCDs) compared to infectious diseases, such as malaria, cholera, AIDS or tuberculosis.(438) In the WHO African Region, non-communicable diseases (NCDs) accounted for 30.7% of disability-adjusted life years (DALYs) in 2015, where five countries (Congo, Ethiopia, Nigeria, South Africa, and Tanzania) accounted for almost 50% of the total DALYs accrued in this region.(439) With regard to the aetiology of productivity losses by cause, NCDs are the most significant cause of productivity losses (37%) in Africa,(440) where MSK disorder is one of the significant contributors to this

NCD burden. However, other diseases such as cardiovascular diseases, cancers and diabetes, have dominated the focus on NCDs, with little attention paid to MSK disorder. This is out of proportion to the impact that MSK disorders have on disability. Studies have shown that although the prevalence of MSK disorders in the LMICs is similar to that in the developed world, the burden is higher.(441, 442) The increased burden is due to delayed diagnosis arising from poor education, sociocultural beliefs, poverty, and limited access to healthcare. To date, most COI studies in MSK disorders are conducted in North African states or South Africa, COI studies in SSA are still sparse.(443, 444)

6.3 Cost-of-illness in LMICs

As detailed in Chapter 2, cost-of-illness summarises the costs of a particular disease to society. This value includes direct costs of treating the disease such as healthcare system costs for diagnosis, treatment and management of disease progression and patients' own expenses (travel, over-the-counter medication), and indirect costs such as productivity loss resulting from time off employment.(390) The information on the COI at a population level helps raise public awareness of policymakers on the economic magnitudes of disease and health conditions for advocacy.(15, 16) A transparent reporting on the costing methods is essential to inform policymakers about the purpose of specific methods, their advantages and limitations, and the extent of variance in estimated costs that can arise from methodological uncertainties. The main challenge in conducting COI studies in LMICs concerns limited and poor-quality resource utilisation data, which are vital requirements for measuring the identified cost items.(54-59) Besides, there is much broader variation in price, and market prices may not accurately reflect the economic value.(445) Moreover, illness experience and health-seeking behaviour are two crucially important issues regarding economic access to health services.(442) In some studies, significant proportions of patients are found to not seek care at healthcare facilities due to financial reasons.(446-

452) As a result, purely considering those costs that arise relative to available household resources may not provide a complete picture of COI. Arriving at an accurate understanding of the household financial burden from chronic illnesses would require representative household surveys that seek information on the financial consequences of health-seeking behaviours.(453)

Economic costs are defined as the full cost borne by society irrespective of who pays for it. On the other hand, financial cost is the actual expenditure paid on the inputs for producing goods and services, reflecting how much money has been spent. Specifically, it "measures of loss of monetary value when a resource is acquired or consumed to carry out an activity."(454) It is primarily used to prepare budgets for financial planning and reporting purposes. Table 6.1 shows the inclusion of cost components depends on the study perspective. As detailed in Chapter 2, direct costs include any direct expenditures associated with illness or accessing care.(1) In contrast, indirect costs refer to the opportunity costs of time incurred by the patient while seeking care and time with reduced productivity due to illness.(82) Ideally, the societal perspective takes into account the comprehensive economic costs and is generally preferred by economists.(4, 5, 14, 103) On the other hand, the payer and employer perspectives only focus on the costs they need to cover from government or insurance schemes. As LMICs usually do not offer comprehensive coverage, people rely on personal healthcare finance. In this context, studies from patients' or societal perspectives would be more appropriate. Indeed, the impact is expected to differ because there is little financial risk protection in many LMICs, and thus financial costs are largely borne by households. However, the societal perspective is often considered not feasible in LMICs due to data availability constraints.(455) Instead, current cost studies in LMICs usually rely on the provider perspective (cost per patient

incurred by the healthcare provider), third party payer perspective or patient perspective.(456-460)

Table 6.1 Costs included in COI studies by perspectives source

Perspective	Direct costs		Indirect costs
	Medical cost	Non-medical cost	
Societal	All costs*	All costs*	All costs*
Payer	Covered costs	Covered costs	
Patient	Out-of-pocket costs	Transportation/ Informal care	Wage losses
Employer			Absenteeism / Presenteeism

* This refers to all costs attributable to an illness, subject to data availability of each study. Source: Luce et al.(102)

Although MSK disorder is one of the significant contributors to this NCD burden, other chronic diseases such as cardiovascular diseases, cancers and diabetes, have dominated the focus on NCDs LMICs.(461, 462) Up till now, COI studies due to MSK in LMICs are sparse and mostly injury or surgery related.(463, 464) Therefore, the following sections discuss the differences in LMICs context and use the 11 studies identified from Chapter 4 as examples.

6.3.1 Identification of Cost Components

Figure 6.1, adapted from McItyne et al.,(442) depicts a pathway of the potential costs incurred by people with an illness and their households. When a person feels ill, they may or may not choose to seek healthcare. If they seek healthcare, they will likely incur some financial costs (direct costs). As presented in Table 6.1, direct costs include medical and non-medical costs. The former is the healthcare expenditures for medication, hospitalisation, outpatient attendance, laboratory tests, rehabilitation, etc. The latter is

related to other expenditures such as transportation, meals and accommodation due to attending a health care provider, home or car adaptation, and informal care.

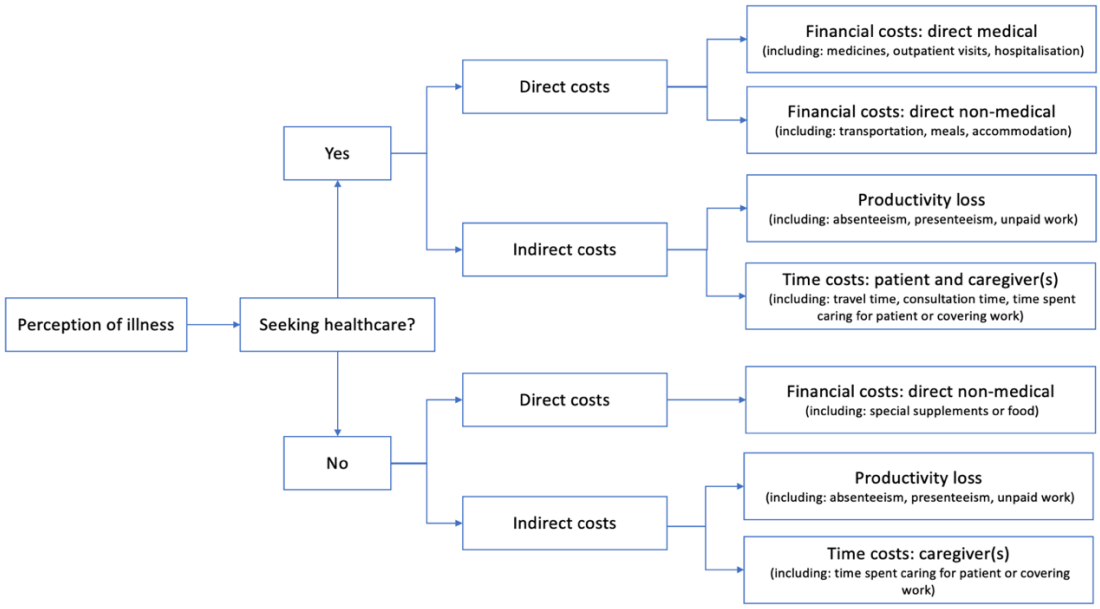


Figure 6.1 Patient cost pathways

Source: adapted from McItyne et al. (442)

People seeking health care will also incur indirect costs. Indirect costs refer to the opportunity costs of time incurred by the patient while seeking healthcare and time with reduced productivity due to illness. It also represents the opportunity cost of time spent by their caregiver(s). If individuals do not seek healthcare, they will avoid direct and indirect costs borne by seeking care; however, they are likely to incur higher costs associated with lost productivity due to illness. They will also likely incur more indirect costs of informal care provided by a family member or friend.(465, 466)

Direct Costs

Without comprehensive health insurance coverage in many LMICs, a literature review by McIntyne and colleagues demonstrates that direct ‘out-of-pocket’ costs, whether to public or private health service providers, can have serious economic consequences for

households.(442) However, due to the often-low prevalence of specific diseases and budgetary constraints in research studies, direct costs data are often pragmatically captured at healthcare facilities rather than as part of a national household survey. Studies are often not nationally representative as they usually are focused on answering specific research questions targeted at a particular population.(467) Among the 11 studies presented in Table 6.2, all cross-sectional studies used convenience samples at study facilities. In this case, sample sizes are often arbitrary and vary widely across studies. Also, the reliance on convenience samples taken from individuals who are seeking and receiving treatment at hospitals, will certainly result in an upward bias in costs for the average person with the condition. Individuals who do not seek care or at a lower level of healthcare facilities, implying lower costs, have no chance of being selected.(461)

Studies differed widely in terms of which costs were included. McIntyre et al. and Russell et al. reported that while direct medical costs are usually included, direct non-medical and indirect costs were sometimes left out of cost estimates.(442, 468) Tanimura et al. and Raban et al. also reported wide variation in cost components.(469, 470) For studies measuring direct costs, Alvarez-Hernandez et al.(354) was the only study from the patient's perspective and thus focused on OOP expenditures on direct medical and non-medical costs. On the other hand, even studies claimed the societal perspective was taken; direct non-medical costs were not always included.(372, 426, 427)

Indirect Costs

Methods for the estimation of indirect costs also vary widely. Absenteeism, including loss of income and/or early retirement, are primarily included in those studies presented in Table 6.2. Most studies measuring absenteeism chose to include the indirect costs of other household members or caregivers, except for one Brazilian study.(425) Presenteeism

relates to reduced productivity at work due to health problems.(87, 88) Almoallim et al. suggested that people who have more ownership over their work schedule may have higher levels of presenteeism in the Middle East and Africa.(471) However, the work environment, functional requirements, and cultural expectations in the working environment may all influence the level of impairment an individual experiences related to work.(444) Moreover, only those in formal sector employment, which is a small minority of the population in LMICs, are likely to have access to paid sick leave benefits.(442) Without the financial risk protection in LMICs, people with MSK disorders may be more reluctant to stay home from work due to illness, and thus, resulting in a higher level of presenteeism. However, none of the 11 studies in LMICs included presenteeism as indirect costs.

In contrast, unpaid work is the production of goods and services that are not sold on a conventional market.(88) As introduced in Chapter 2, three main types of activities can be distinguished, including household work, care work, and volunteer work.(98) These could be the tasks and activities of daily life that people do to occupy themselves and fulfil specific purposes such as self-care, productivity, and leisure.(472) People living with MSK disorders experience symptoms that limit their daily activities, including leisure, housework, caregiving, and employment.(473-475) Globally, women undertake three times more care and domestic work than men, with women in LMICs devoting more time to unpaid work than women in high-income countries.(99) However, equity-related differences within countries also exist. The amount of unpaid work varies greatly between those in HICs and LMIC and between different income groups within countries.(476) People with high incomes, irrespective of HIC or LMIC, are able to outsource more onerous household chores, for example, by using care services and domestic help. In contrast, people who lack financial protection are often burdened by repetitive, time

consuming, and physically demanding domestic tasks.(99) Furthermore, people with higher socioeconomic status may have the privilege to choose and select certain occupations, while people with lower socioeconomic status face greater barriers to engaging in desired occupations.(473, 477, 478) Although unpaid work was not included in these studies, Osiri et al. and Xu et al. attempted to value household work for people who were not in paid work.(345, 372)

Table 6.2 Study characteristics: cost-of-illness studies in RA in low- and middle-income countries

	Aggarwal et al. 2006	Alvarez-Hernandez et al. 2012	Baser et al. 2013	Chermont et al. 2008	de Azevedo et al. 2008	Hu et al. 2018
Country	India	Mexico	Turkey	Brazil	Brazil	China
Classification by the World Bank	LMIC	UMIC	UMIC	UMIC	UMIC	UMIC
Study design	Cross-sectional survey	Cross-sectional survey	Retrospective cohort analysis	Cross-sectional survey	Cross-sectional survey	Cross-sectional survey
Perspective	Not reported	Patient	Not reported	Societal	Societal	Societal
Sampling for cost data	Convenience sample at study facility	Convenience sample at study facilities	Health insurance database	Convenience sample at study facility	Convenience sample at study facility	Convenience sample at study facilities
Location of interview	RA clinic	RA clinics	NA	RA clinic	RA clinic	RA clinics
Sample size	101	320	1920	100	192	133
Direct costs	medicines, laboratory tests, transportation	medicines, hospitalisation, outpatient visit, alternative therapies, laboratory tests, transportation and meals	medicines, outpatient visit, hospitalisation, healthcare personnel, laboratory tests, devices and adaptation	medicines, outpatient visit, hospitalisation, laboratory tests, devices and adaptation, transportation	NA	medicines, outpatient visit, hospitalisation
Indirect costs	loss of income, home help	work disability, home care, loss of income	NA	NA	absenteeism, early retirement	absenteeism (patient and caregiver), early retirement
Recall period (costs)	1 year	6 months	NA	Not reported	The last month and last year	3 months

	Malhan et al. 2010	Malhan et al. 2012	Osiri et al. 2007	Osiri et al. 2013	Xu et al. 2014
Country	Turkey	Turkey	Thailand	Thailand	China
Classification by the World Bank	UMIC	UMIC	UMIC	UMIC	UMIC
Study design	Cost data from literature review	Expert panel (rheumatologists)	Cross-sectional survey	Retrospective cohort analysis	Cross-sectional survey
Perspective	Payer	Societal	Societal	Societal	Societal
Sampling for cost data	Sample taken from a reference article	NA	Convenience sample at study facility	Convenience sample at study facility	Convenience sample at study facilities
Location of interview	NA	NA	RA clinic	NA	RA clinics
Sample size	562	NA	158	684	829
Direct costs	medicines, outpatient visit, hospitalisation, laboratory tests, devices and adaptation	medicines, outpatient visit, hospitalisation	medicines, hospitalisation, laboratory tests, alternative therapy, rehabilitation, devices and adaptation, transportation and meal, household help	medicines, outpatient visit, laboratory tests, radiologic examinations	medicines, outpatient visit, hospitalisation, laboratory tests, alternative therapy, devices and adaptation, transportation and meal, household help
Indirect costs	NA	absenteeism (patients and caregiver), work disability, early retirement, early death	absenteeism (patient and caregiver)	NA	absenteeism (patient and caregiver), early retirement
Recall period (costs)	NA	NA	8-12 weeks	NA	year

Abbreviations: LMIC= lower-middle-income country; RA= rheumatoid arthritis; UMIC=upper-middle-income country

6.3.2 Measurement of COI

In order to increase standardisation and comparability across studies, it may be advisable to use validated questionnaires to collect data about COI.(98, 479) However, systematic reviews of existing COI studies in LMICs highlight various data collection approaches across cost components, data sources, sampling methodologies and recall periods.(442, 461, 469, 480, 481) In part, this heterogeneity may stem from limited practical guidance or standards on collecting COI data, particularly in the LMIC setting with more constraints. To date, there is a lack of comprehensive instruments to collect data on COI in LMICs.(437)

Typically, resource use can be collected through diaries, review of administrative records, survey questionnaires, and use of expert panels. Although a review of administrative records is less costly in time and resources, it is also less likely to include non-institutional costs, for example, non-medical and indirect costs.(357, 429). Several potential biases are associated with the estimation of resource use, including recall error, respondent error, telescoping error, and survey fatigue.(482) These potential errors are also applicable to the estimation of indirect costs. Survey design is vital to reduce the likelihood of these errors.

If adequately filled, the diary method of recording expenditures is considered the ‘gold standard’(482) as it is a good way to track household costs between follow-up visits. Also, it reduces the potential for recall errors. However, poor adherence is common when using the diary method, and it may not be appropriate in settings with low literacy rates.(483)

Recall error refers to the inverse relationship between the length of time over which survey respondents are asked to recall something and the accuracy of the estimates.(484) Recall has often been regarded as the ‘second best’ option in measuring expenditure. It has also

long been recognised that the timing of the recall period can have a significant impact on answers to questions on expenditure.(485) Generally, a shorter recall period will result in higher estimates due to telescoping bias. Lu et al.(486) found that more detailed questionnaires and shorter recall periods resulted in higher estimates of OOP payments. However, short recall periods can also be problematic: some expenditures may be seasonal, affecting the accuracy of cost estimates if not captured in the correct period. Of the 11 studies in Table 6.2, the reported recall periods ranged from 8-12 weeks to 1 year. Most studies had only one interview with participants, except for the study by Osiri et al. (every 8-12 weeks) undertaken in Thailand.(372)

Respondent error is the inability to accurately capture expenditure by other household members of the survey respondent. This is most problematic where the respondent was not the financial respondent who made the payments.(487, 488) Survey fatigue occurs where survey length is exceptionally long, and respondents are tired of answering detailed questions. Fatigue can also impact data collection through diaries, where respondents stop recording expenditures.(489)

6.3.3 Valuation of COI

Direct Costs

To value direct costs, researchers often multiply the quantity of resource utilisation by participants with relevant unit costs. In the context of LMICs, one of the major challenges is obtaining unit cost information.(454, 490) Moreover, there is much broader variation in price, and market prices may not accurately reflect the economic value of resources.(445) Therefore, the transparency of reporting the costing methods and unit costs is vital for readers and policymakers to interpret the cost estimates. On the other hand, when the focus

of the COI study is on the actual financial impact of health-related costs on the household, direct costs of the actual money paid for goods and services is appropriate.

The valuation of direct costs is susceptible to the same types of survey error as the data collection; respondents may not accurately recall the amount they paid for a consultation or transportation to a healthcare facility, especially if this took place a long time ago.

Indirect Costs

As detailed in Chapter 2, the human capital approach (HCA) and friction cost approach (FCA) are two competing approaches commonly used to value indirect costs. The FCA only values the estimated actual production lost during the time it takes to replace the sick worker, known as the 'friction period', while the HCA is generally taken to reflect lost productive potential. Although the HCA has been criticised for overestimating the true productivity loss, the FCA requires more data, for example, the friction period and unemployment rate. In addition to data availability, the FCA may be not feasible in LMICs as informal employment is more common. For example, other family members frequently fill in for a sick person during the planting season in agriculture so that the same area of land is planted despite the illness.(491) The literature on COI studies in developing countries recognises that the majority of studies use the HCA.(345, 354, 357, 425, 426)

Although the loss of income is relatively intuitive and convenient to be used in indirect costs, a widely recognised challenge is that informal employment is common, and income is often seasonal in LMICs.(60, 61) Therefore, it is still uncertain whether the approaches to valuing indirect costs which were developed for a HIC setting are also relevant to a LMIC setting where the labour market operates quite differently. The FCA has not been tested in a LMIC to date,(492) and the value of informal care and unpaid work may be

valued differently in settings where there is high unemployment. There is a great need for further consideration of how to apply the lessons learned in a HIC setting to LMICs.

6.4 The Development of Methodology for Conducting a COI of MSK in Tanzania

The following sections present the development of a COI study for MSK in Tanzania, considering the methodological challenges outlined above and addressing these to develop a context-specific questionnaire.

6.4.1 Identification of Pre-existing Questionnaires

As described in Section 6.3.2, although using validated questionnaires to collect data about COI could increase standardisation and comparability across studies, there is a lack of comprehensive instruments in LMICs. Therefore, this section identifies currently available tools for capturing relevant direct and indirect costs. Following this, the development of the COI questionnaire will then build on the evidence generated from the systematic review for global COI studies in RA that was identified in Chapter 4.

Details on the methodology and results of studies were presented in Chapter 4. Of the five identified instruments (Table 6.3), the Work Productivity and Activity Impairment Questionnaire (WPAI-RA)(493), WHO Health and Work Performance Questionnaire (HPQ)(143) and Health and Labour Questionnaire (HLQ)(494) are validated instruments for measuring indirect costs, while the Cost Assessment Questionnaire (CAQ)(495) and Health Economic Questionnaire (HEQ-RA)(496) include both direct and indirect costs. Ten included studies estimated the COI in RA using a self-reported questionnaire survey.(62) Seven of the ten studies used validated instruments to inform their COI; all were conducted in HICs.

Compared to direct costs, indirect costs were mostly measured by validated instruments. Absenteeism is calculated by asking the respondents to quantify the number of hours/days lost due to health problems. In the HLQ, absenteeism is measured by workdays loss in the past week by filling a diary, where the HPQ and WPAI-RA measured the workhour loss in the past week.(143, 493, 494) On the other hand, presenteeism is the self-perception of their work performance by using a Likert scale or visual analogue scale (VAS).(143, 493, 494)

Although the advantage of adopting validated instruments is to increase the standardisation and comparability of cost estimates across studies, researchers may need to adjust some questions to account for heterogeneity in demography, epidemiology, or resource utilisation in different settings.(497, 498) In LMICs context, for example, healthcare infrastructure and labour market are very different from HICs, it may be more feasible to develop a tailored questionnaire for estimating COI.

Table 6.3 Cost instruments identified from the systematic review for cost-of-illness studies in RA

Category	Tool	Author/Year/ Country
Both direct/ indirect	Cost Assessment Questionnaire, the economic component of the Stanford Health Assessment Questionnaire (HAQ),(495) modified for the Canadian context	Fautrel, 2007, Canada(347)
Both direct/ indirect	Health Economic Questionnaire (HEQ-RA)(496)	Merkesdal, 2005, Germany(337)
Indirect cost	WHO Health and Work Performance Questionnaire (HPQ)(143)	Kessler, 2008, USA(105)
Indirect cost	Health and Labour Questionnaire (HLQ)(494)	Sogaard, 2010, Denmark(351)
Indirect cost	Work Productivity and Activity Impairment Questionnaire (WPAI-RA)(493)	Kruntoradova, 2014, Czech(332) Radner, 2014, Austria(336) Sruamsiri, 2017, Japan(352)

Grey Literature

Furthermore, it is known that major drivers for patient costs can vary by setting and across income quintiles,(469, 499) making it challenging to pre-suppose any exclusions or the relative attention placed on each aspect of expenditure or income measured. In addition to inspecting the instruments identified from the systematic review, several resources that were potentially suitable for the Tanzanian context were advised by the local collaborator and senior health economists in the GHRG – Arthritis study. These government reports and relevant questionnaires in the African setting include the Demographic and Health Surveys (DHS),(500) Tanzania National Panel Survey (NPS)/ Living Standards Measurement Survey,(501) INDEPTH Health Equity Tool for measuring socioeconomic status.(502) The Tanzania DHS and NPS questionnaires were adopted to design questions regarding demographics (e.g. district/village, religion, marital status and education), household characteristics, health-seeking behaviours (e.g. type of healthcare providers, journey and distance to healthcare facilities). The INDEPTH Health Equity Tool was used to design questions for living standards, such as wealth (including the list of assets, animals and cattle), income, and food/financial security.

6.4.2 General Structure of the COI Questionnaire

Overall, questions were categorised into two major categories: 'Cost-of-illness' and 'Living standards.' (Table 6.4, see the whole questionnaire in Appendix E) As discussed in Section 6.3, due to the nature of health financing in developing countries, evidence shows a strong positive relationship between living standards and health care utilisation with heavy reliance on OOP payments.(503) Hence, information on living standards was included in this COI questionnaire to understand the study participants better and put the results into context. For example, questions regarding income sources, categories of monthly household income, and the ownership of assets and livestock were adopted from

grey literature that have been used in Tanzania.(501, 502) For the COI part, questions regarding direct and indirect costs were embedded in ‘Health’ and ‘Labour’. On the other hand, living standards were categorised in ‘Income’, ‘Wealth’, and ‘Other.’

Direct Costs

In the ‘Health’ section, direct costs consisted of visiting a health care provider, hospitalisation, transportation, and health-related OOP expenditure. Visits to healthcare providers in the past three months were measured using a binary choice. Details on the type of healthcare provider and frequency, transportation to the facility, time, and self-reported price for each journey will be further acquired if the respondent had any visit. The Tanzania National Panel Survey was used to identify the types of healthcare providers.(501) Similar questions were designed for hospitalisation and traditional healers. However, a longer recall period of 12 months was adopted in order to capture relevant events. The type of illness or injury that led to their hospitalisation(s) followed the above questions. Moreover, the respondent would be asked to provide self-reported payments spent on the hospitalisation(s), including estimated values of any in-kind payment. Additionally, household expenditures on health in the past four weeks were included.

Indirect Costs

Indirect costs included absenteeism and presenteeism in paid work and the impact on daily activities. To understand the impact on productivity loss in paid work, questions in the ‘Labour’ section started with a broad category to identify whether they worked as an employer, ran a non-farm business, or only worked on household agricultural activities in the last 12 months. Further, the respondent was asked to provide the primary and secondary economic activities they spent most of the previous three months.

In addition to workhour loss due to health problems in the preceding seven days that is commonly used for measuring absenteeism in validated instruments,(143, 493, 494) total days working in this job and the weekly average hours for the last three months were asked for to provide a better understanding of their economic activities. Similar to the WPAI-RA,(493) the respondent was asked to evaluate the impact on their work performance and "home-based" daily activities due to health problems in the last seven days by a VAS. While the work performance was regarding presenteeism in paid work, "home-based" daily activities (e.g. walking, dressing, cleaning, collecting firewood, collecting water, cooking etc.) were specified to exclude primary and secondary economic activities. In the VAS, '0' means the health problem had no effect on their work, and '10' means the health problems completely prevented them from working.

Table 6.4 Key questions in the cost-of-illness questionnaire

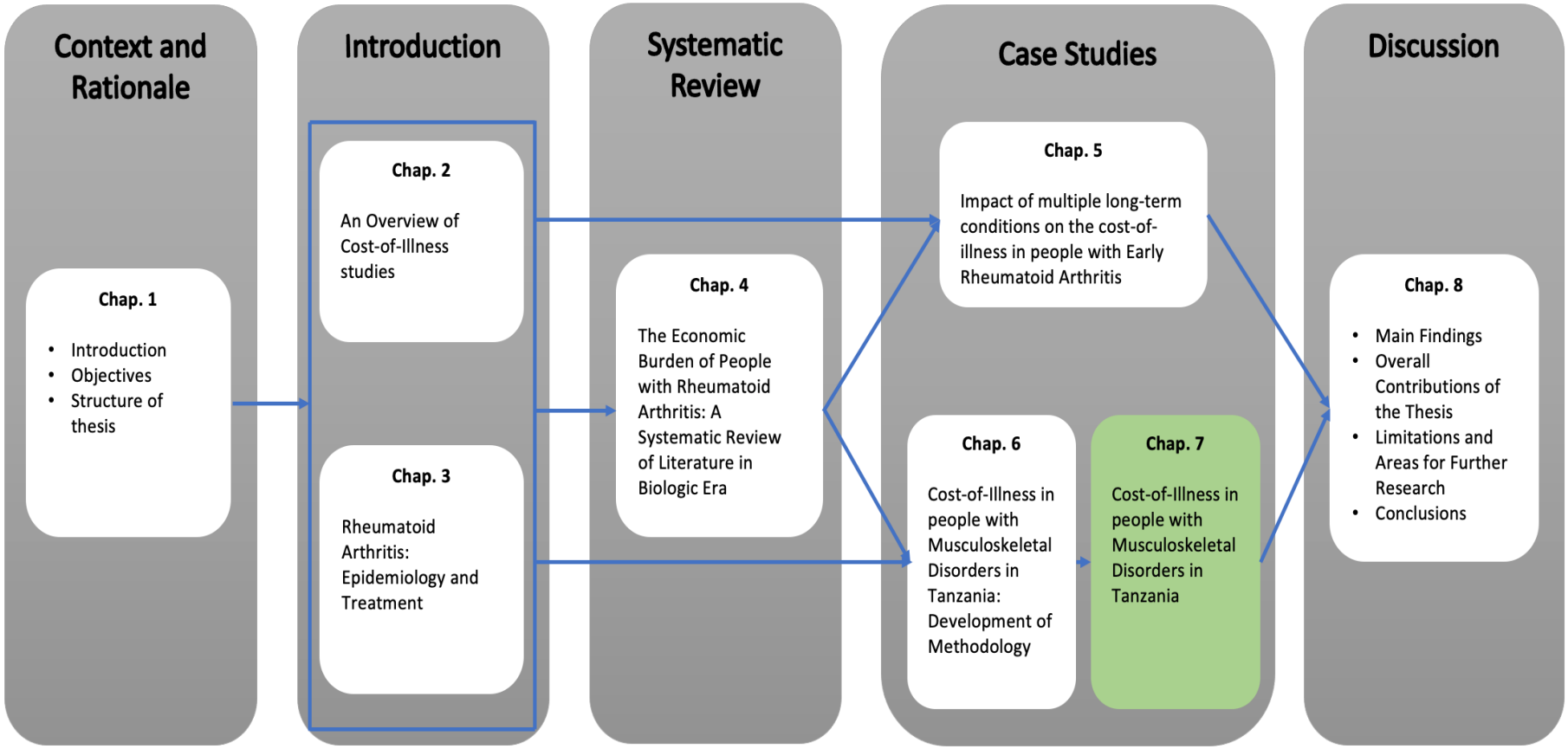
Category	**Cost-of-illness**		**Living standards**		
	Direct costs	**Indirect costs**			
Section	**Health**	**Labour**	**Income**	**Wealth**	**Other**
Key questions	Visit to healthcare providers Hospitalisation No. of overnight stays Self-reported cost Distance to hospital/transportation Visits to traditional healer	Employment status Primary/secondary activity Work hours/week Time missed because of health problems Health problems affecting work/daily activities	Main sources of cash income Household monthly income (wage/business) Self-reported assessment of financial circumstances: now/2 years ago	Assets Land Animals Money/goods borrowed: amount/reason	Unforeseen circumstance (past 2 years); severity Food security (last 12 months/yesterday/next 3 or 4 months
Respondent	**Identified individual/proxy household member**		**Financial respondent**		

6.5 Chapter Summary

This chapter presents and discusses different methodological challenges when conducting COI studies in LMICs. The case studies in LMICs from the systematic review for COI studies in RA in Chapter 4 were used to inform critiques of existing COI studies in LMICs. Although a few COI studies in RA have been conducted in middle-income countries, none was found in LICs or Africa. In addition to data availability, conceptual challenges regarding what should be included in COIs in LMIC settings, as this will not be the same as in HICs. For direct costs, OOP spending is recognised as an essential barrier to accessing healthcare in LMICs. In indirect costs, informal employment is common, and income is often seasonal in LMICs. It is still uncertain whether the approaches to valuing indirect costs which were developed for a HIC setting are also relevant to a LIC setting where the labour market operates quite differently. Therefore, questions regarding absenteeism were not limited to the past seven days but also extended to total days working in the previous three months in this COI questionnaire.

Although using validated questionnaires to collect data about COI could increase standardisation and comparability across studies, some flexibility may be required as the context and data availability vary. Given the healthcare infrastructure and labour market in LMICs are quite different from HICs, it may be more feasible to develop a tailored questionnaire for estimating COI, accounting for heterogeneity in demography, epidemiology, or resource utilisation in different settings.

This chapter highlights the need and complexity for conducting a COI study of MSK in LMICs and aims to address the evidence gap. It also discusses the methodological issues for conducting a COI study in LMICs and presents the development of methods for this empirical study. The next chapter will deliver the data analysis and results of the COI.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CHAPTER 7. COST-OF-ILLNESS IN PEOPLE WITH MUSCULOSKELETAL DISORDERS IN TANZANIA

7.1 Introduction

As highlighted in Chapter 6, there is a distinct lack of cost-of-illness (COI) studies in rheumatoid arthritis (RA) and musculoskeletal (MSK) disorders in low- and middle-income countries (LMICs), particularly in Africa. Eight of eleven COI studies in RA that have been conducted in middle-income countries were based on convenience samples taken from individuals seeking and receiving treatment at hospitals,(345, 354, 357, 372, 425, 426, 428, 430) except for three studies used data from expert opinions,(427) literature review(431) and retrospective analysis from health insurance database.(429) Individuals who do not seek care or at a lower level of healthcare facilities, implying lower costs, are unlikely to be included in these studies. With regard to productivity losses by cause, NCDs are the most significant cause of productivity losses (37%) in Africa,(440) where MSK disorder is one of the significant contributors to this NCD burden. However, other diseases such as cardiovascular diseases, cancers and diabetes, have dominated the focus on NCDs, with little attention paid to MSK disorder. This is out of proportion to MSK disorders' impact on disability. The measurement and valuation of broader aspects of MSK are important to inform policy development on disease prevention and management, as well as the need for healthcare services.

Apart from data availability, conceptual challenges in terms of what should be included in COIs in LMIC settings should also be taken into account as this will differ from those undertaken in high-income countries. Moreover, as LMICs usually do not offer comprehensive healthcare coverage, financial costs are largely borne by households. Other financial barriers, such as inaccessible health care and transportation, may also prevent

people from seeking care. As a result, purely considering those costs that arise relative to available household resources may not provide a complete picture of COI.

This chapter firstly aimed to develop a COI study in people with MSK disorders by using primary data collection in a low-income setting, building on the COI questionnaire developed for the Tanzanian context as introduced in Chapter 6. Given the lack of available data on anticipated costs/categories in this low-resource setting, a control group of people without the condition could provide useful information to interpret the implications.(157, 461, 504) In order to elucidate the findings, it was decided that a control group without MSK would be useful. Secondly, scenario analyses were conducted to explore the uncertainty around the health-seeking behaviour and household OOP expenditures on health to understand the impact from a societal perspective.

7.2 Methods

This COI study was embedded in a cross-sectional community survey in the Global Health Research Group (GHRG) – Arthritis study, funded by the National Institute for Health Research (NIHR).[2] This component of the empirical study aimed to estimate the COI in people living with MSK in Tanzania from a broad societal perspective.

7.2.1 The Tanzanian Context

Tanzania is located in East Africa, bordering the Indian Ocean, between Kenya and Mozambique. It covers an area of 945,090 square kilometres, with a population of 58 million and a population growth rate of 2.94% per annum.(505) Agriculture is the primary

[2] NIHR Global Health Research Group on estimating the prevalence, quality of life, economic and societal impact of arthritis in Tanzania: a mixed methods study at the University of Glasgow
Funding: National Institute for Health Research (NIHR) UK Government (Project 17/63/35)
Funding stream: Global Health Research Fund (ODA, DAC LIST LMIC) Project term 1st April 2018 - 31st March 2022, Budget £2,493,273

economic sector, with almost 50% of the labour force employed on their own farms.(506) However, weak infrastructure and communications and dependence on rainfed cultivation mean the sector is comparatively under-developed.(507) Outside of agriculture, three-quarters of paid and self-employment opportunities are in the informal sector, with more women (an estimated 82% of informal sector workers) than men (72%).(508) The GDP in 2019 was $ 62.24 billion,(509) with an estimated per capita expenditure on health of $37, including OOP expenses.(510)

The Tanzanian health system is decentralized, including government and private health facilities, pharmacies and drug retailers, and a variety of traditional or religious healers.(511) Over 80% of health facilities are government-owned hospitals and health centres. Over-the-counter drugs are widely available from private shops and kiosks.(512) The government system has a pyramidal structure and comprises three functional levels: district, regional, and referral hospital. At the district level, dispensaries, health centres, and district hospitals provide primary health services and refer to secondary, regional hospitals when needed. Larger referral hospitals exist to provide tertiary care based on referrals from lower levels of care.(511)

The primary provider of health insurance is the National Health Insurance Fund (NHIF), which was established by an Act of Parliament (No. 8) in 1999 but became operational in 2001. The scheme, which was initially meant to provide cover for those who work in public sectors, currently also enrols people in the private sector.(513) Contributions by private members into the NHIF are voluntary and cover mostly salaried workers on an individual basis or as employees of registered private employers.(513) Overall, health insurance coverage is still low in Tanzania. Across all schemes, there is only a 16% level of coverage of health insurance in Tanzania.(514) Low insurance coverage leads to heavy

reliance on direct payment at the point of health care utilisation, which is among the fundamental problems that restrain the move towards universal health coverage in many LMICs.(515) Direct payment can lead to a high level of inequity and, in most cases, deny the poorest access to health care.(516) In addition, a significant deficit in doctors providing healthcare was reported in the country, with the ratio of 1.4 doctors per 100,000 population falling largely behind the WHO recommendation.(517)

7.2.2 Study Design

In this case study, the author designed the COI questionnaire (as presented in Chapter 6, Section 6.4) with inputs from Emma McIntosh, Manuela Deidda and Eleanor Grieve. The COI queationnaire was further embedded in the health economic questionnaire for the community survey. The author also designed and conducted the COI analysis of this study.

Study site and sample

The cross-sectional community survey was conducted in the Hai district in the Kilimanjaro region of Tanzania from January to September 2021. The Hai district includes 67 villages. Two of the villages, Tindigani and Mtakuja are excluded, given the possible confounding between fluoride poisoning and arthritis symptoms. One additional village in Moshi Urban (Majengo) was also included in the community survey, in order to perform an exploratory analysis in this district.

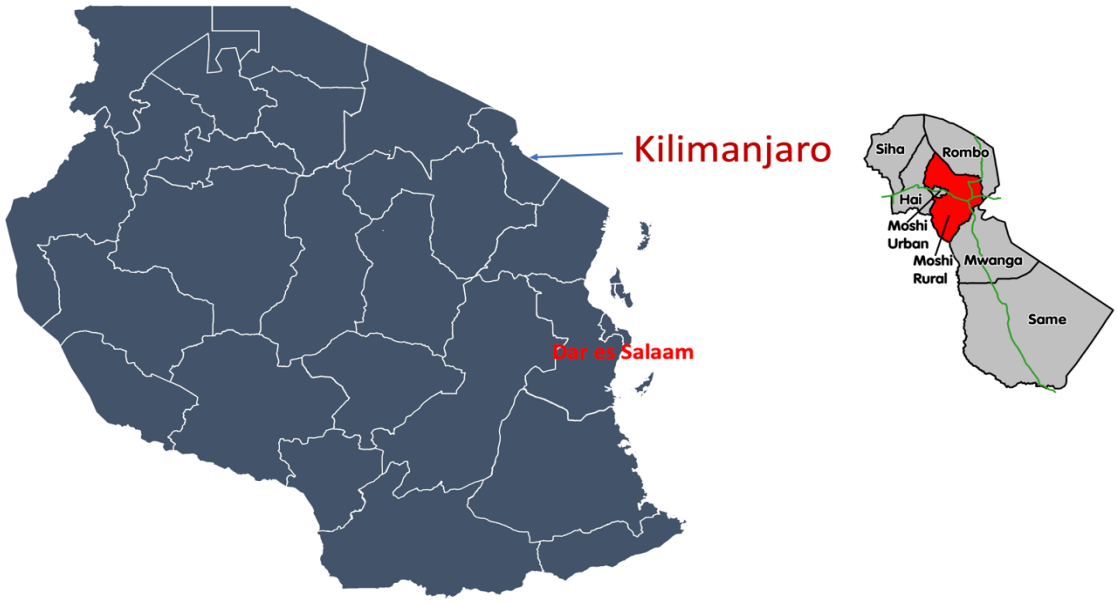


Figure 7.1 Map of study site in the Kilimanjaro region, Tanzania

Two-stage sampling has been selected as the most suitable strategy in terms of feasibility in the Tanzanian context and statistical robustness for the community survey. In the first stage, villages were selected as the primary sampling units (clusters), which were sampled proportional to their sizes. In the second stage, households were selected with random probability as the secondary sampling units. Using households as secondary sampling units is in line with the sampling strategy which is commonly used by the Tanzania national Bureau of Statistics, and is thus a feasible option in this context. As a result, 1,095 households, which correspond to approximately 2,750 individuals, were sampled. Residents aged over five years and living in the selected households for six months or more were eligible for this study.

Identification of MSK Disorders

Through the tiered approach (see Figure 7.2) in the community survey, the Gait Arms Legs Spine (GALS), the paediatric Gait Arms Legs Spine (pGALS) and the Regional Examination of the Musculoskeletal System (REMS) were used to assess the prevalence of

MSK disorders in the population. GALS have been shown to be highly sensitive in detecting abnormalities of the MSK system.[1] The standard GALS involves three screening questions and a brief screening assessment of Gait, Arms, Legs and Spine, taking approximately 3-5 minutes to perform. Once a potential MSK abnormality had been detected by the GALS/pGALS, a further clinical screening examination by the REMS in Tier 2 was carried out to ascertain whether these problems may be related to joint pains. REMS involves examining a group of joints linked by function and may sometimes require a detailed neurological and vascular examination. GALS negative participants were asked about their willingness to join the control group. When a REMS positive case was identified, two control cases of the same age and within +/-3 years from the case were randomly selected in the database and revisited. The developed COI questionnaire was answered by participants with REMS positivity (MSK group) in Tier 3 and those in the control group.

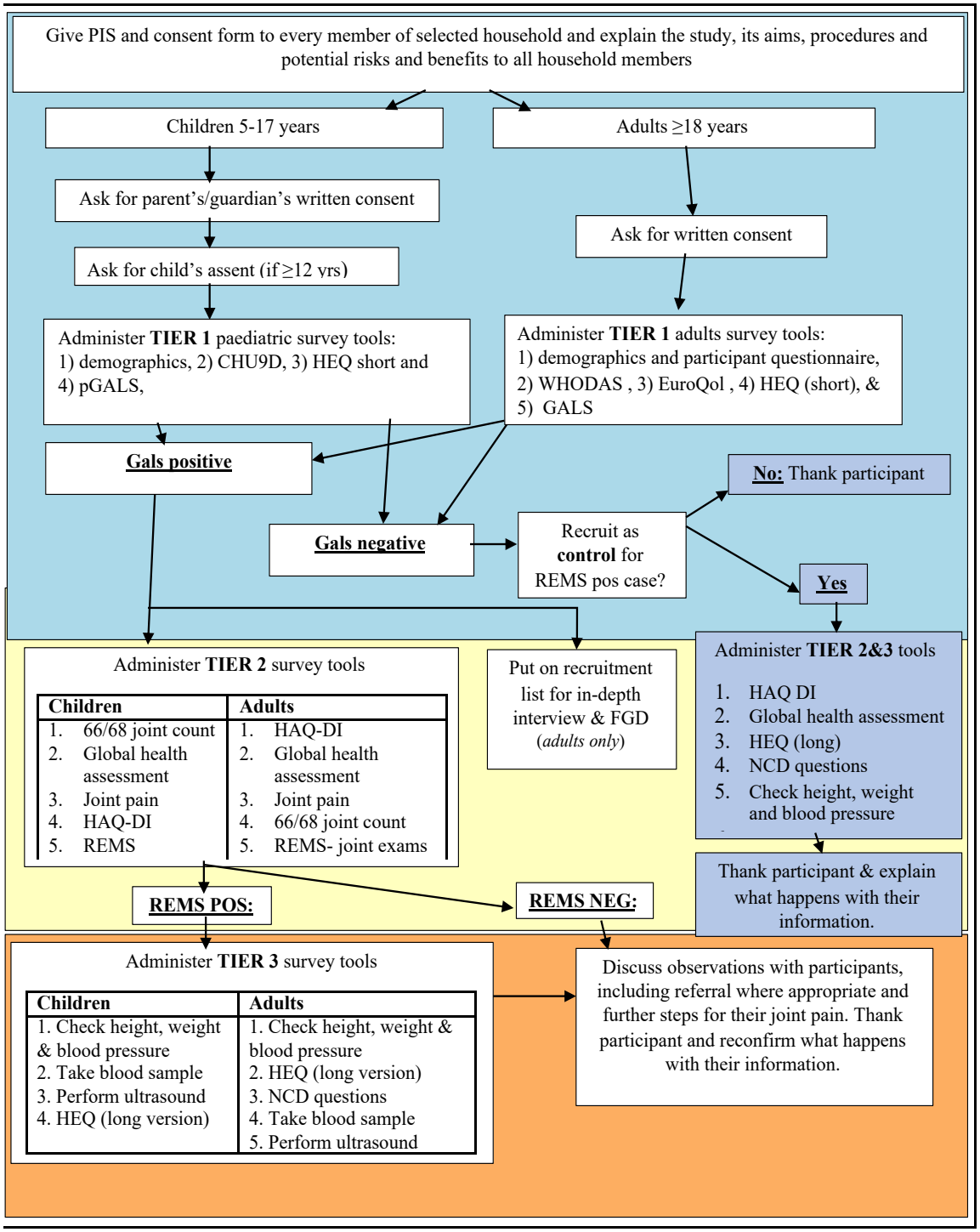


Figure 7.2 Tiered approach adopted from the NIHR GHRG-Arthritis study

Among the 2,750 individuals screened, 21 participants had problems that were detectable with the GALS exam but were not of MSK origin (e.g. neurological issues, post-polio disease etc.), and 6 participants were unable to perform the GALS exam and thus excluded. For the 227 participants with GALS positivity, 159 were REMS positive and included in the MSK group accordingly, while 467 out of 2,496 GALS negative participants agreed to join the control group (Figure 7.3).

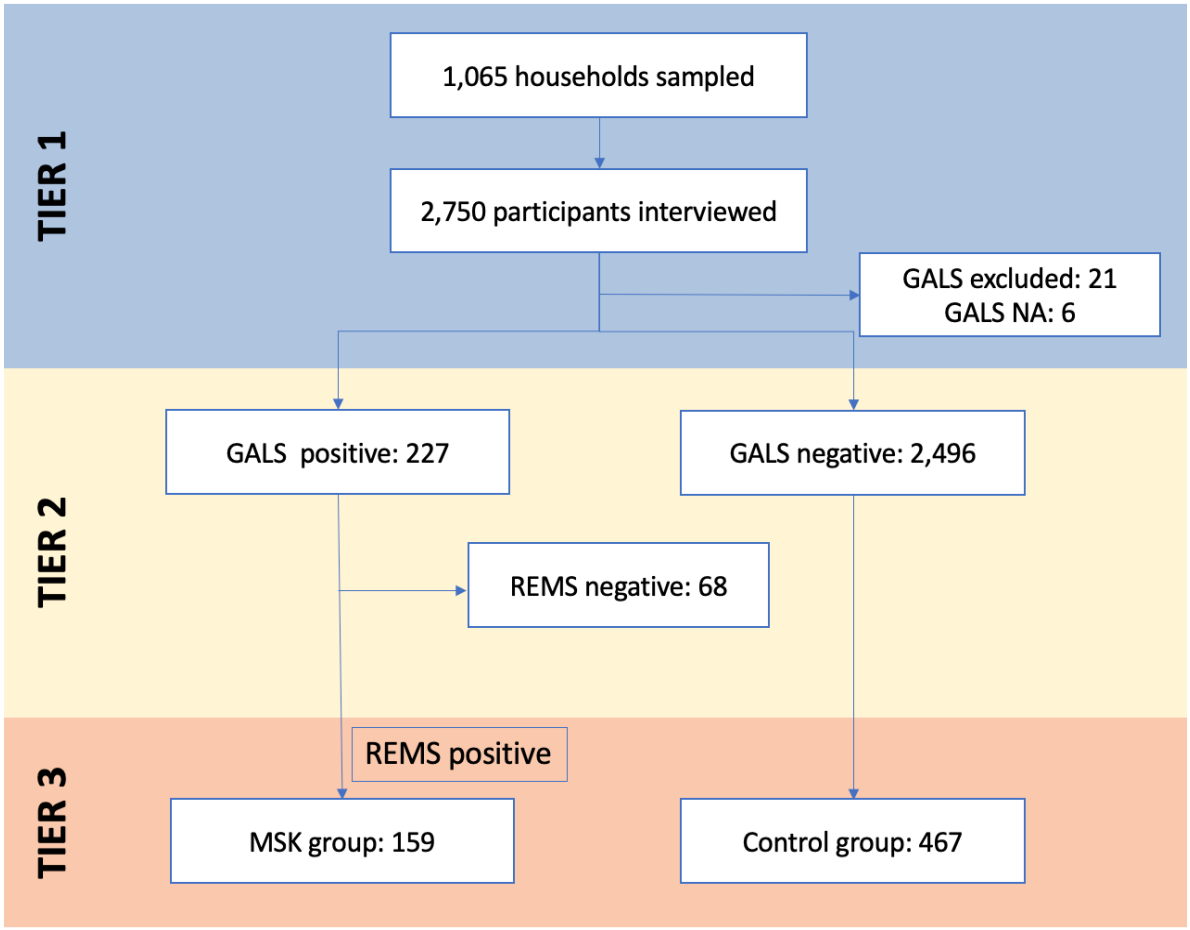


Figure 7.3 Study flowchart

7.2.3 Data Collection and Management

A team of local interviewers were trained on the study's concepts and methods and how to conduct the interviews. In addition to clinical assessment of GALS/pGALS and REMS, demographics and COI data using the developed COI questionnaire were collected during the household interview. The data collection for this COI study was all interview-based. The COI questionnaire was developed in English, translated into Swahili (local language) for use in the community survey. All data were uploaded into the Open Data Kit (ODK) platform and then exported to Microsoft Excel for verification and further analysis.

7.2.4 Definitions and Cost-of-Illness Method

The COI method consisted of three steps: identification, measurement, and valuation. The identification and measurement of cost components were described in the development of the COI questionnaire in Chapter 6. In terms of valuation, economic costs defined as the full cost borne by society were included irrespective of who pays for it.(454) This COI study used a bottom-up approach to estimating the COI in people with and without MSK disorders from a societal perspective. Quantities of resources were estimated from the COI questionnaire and then assigned prices to reflect the value of those resources.

As introduced in Chapter 2, COI studies can be described as prevalence-based or incidence-based approaches based on the way in which the epidemiological data are used. The former approach estimates the economic burden due to a health condition over a specific period, while the latter estimates the lifetime costs of a condition from its onset until its disappearance.(82) With the nature of long-lasting conditions such as MSK disorders requiring considerably lengthy follow-up periods, the prevalence-based approach is more practicable to measure than the incidence-based approach.

As outlined Section 7.1, given the lack of available data on anticipated costs/categories in this low-resource setting, a control group of people without the condition could provide useful information to interpret the implications.(157, 461, 504) It is expected that self-reported costs, even from random samples of patients, are likely to be biased upwards when there are no controls.(157) Some of the people with the condition would have incurred some health expenses in any case and this can only be captured by including controls without the condition. This issue is particularly important when considering indirect costs in an LMIC setting, where informal employment is common and income is often seasonal.(60, 61). In order to elucidate the findings, it was decided that a control group without MSK would be useful.

Estimation of Direct costs

The identification and measurement of direct costs was introduced in Chapter 6 (Section 6.4.2). In the 'Health' section, direct costs consisted of visiting a health care provider, hospitalisation, transportation, and health-related OOP expenditure. Direct costs were defined as the sum of medical and non-medical costs. Resource utilisation includes visits to the healthcare provider in the previous three months and hospitalisation during the last 12 months. Costs for visits to the healthcare providers were calculated by multiplying the sum of frequency, with differentiated unit costs by the levels of healthcare provider. On the other hand, costs for hospitalisation were calculated by multiplying the length of hospital stay with the unit cost of a bed day in a primary hospital, given the hospital level was unavailable.(518)

Unit cost data for visits to the healthcare provider and an inpatient bed day were derived from the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) project (Table 7.1) at 2010 International Dollars (I$) in Tanzania.(518) The WHO has estimated unit cost

values for service delivery at the country and regional level, which can be considered 'average' values of unit costs. The unit cost for a visit to the healthcare provider presents the estimated cost per outpatient visit, including all cost components except drugs and diagnostics. Similarly, the unit cost for an inpatient bed day excludes the cost of drugs and diagnostic tests but includes personnel, capital and food costs. Unit costs were inflated to 2020 by Tanzania's consumer price index (CPI).

Self-reported financial costs, including the price for each journey to the healthcare facility and health-related expenditures in the past four weeks were collected in the COI questionnaire. Costs spent on travelling were calculated by multiplying the sum of visits to healthcare facilities, with self-reported price for each journey. The health-related expenditures were considered as the household OOP expenditures in the analysis.

Table 7.1 Unit costs of inpatient and outpatient health service and average wages by economic sectors

Cost item	Unit costs in International Dollar (Inflated to 2020)
Health resource in Tanzania *Source: WHO-CHOICE**	
Outpatient visit$^{\Psi}$ – health centre	3.58
Outpatient visit – primary	3.58
Outpatient visit – secondary	5.09
Outpatient visit – tertiary	5.19
Inpatient hospital bed day$^{\rho}$ – primary	17.12
Average daily wages, Tanzania *Source: Ministry of Labour and Employment*	
Agriculture services	5.94
Trade, Industry and Commerce	6.84
Other	5.94

* WHO-CHOICE: CHOosing Interventions that are Cost-Effective, World Health Organisation$^{\Psi}$ Unit cost for visit to health provider including all cost components for an outpatient attendance, except for drugs and diagnostics. $^{\rho}$ Unit cost for inpatient bed day includes costs such as personnel, capital and food costs, but excludes the cost of drugs and diagnostic tests.

Estimation of Indirect costs

As introduced in Chapter 6 (Section 6.3.2), indirect costs consisted of paid work, including absenteeism, presenteeism, and unpaid work. To understand the impact on productivity loss in paid work, questions in the 'Labour' section started with a broad category to identify whether they worked as an employer, ran a non-farm business, or only worked on household agricultural activities in the last 12 months. Costs for absenteeism were calculated by multiplying the self-reported workday loss due to health conditions in the last seven days with average wages.

Absenteeism:

$$Productivity\ loss\ due\ to\ absenteeism\ (per\ week) = Number\ of\ days\ missed\ due\ to\ health\ problems\ \ (last\ week) \times\ Daily\ wage$$

Although it is recommended to use average age- and gender-specific wage rates unless these are not representative of the potential patient population,(98) the average age- and gender-specific wage rates were not available. Alternatively, average wages differentiated by types of economic activities published by the Ministry of Labour and Employment in Tanzania (Table 7.1) were used in this context. The average wages were inflated from the base year 2010 to 2020 by the CPI in Tanzania and then converted to International Dollars by the purchasing power parity.

In the developed COI questionnaire, presenteeism was measured by self-evaluation of the ability to work affected due to health problems in the past seven days, which was adopted from the Work Productivity and Activity Impairment Questionnaire (WPAI-RA).(493) In the 10-point visual analogue scale, '0' means the health problem had no effect on their

work, and '10' means the health problems completely prevented them from working. To value productivity loss due to presenteeism, it is necessary to calculate the percentage of absenteeism. Accordingly, productivity loss due to presenteeism could be estimated based on the affected performance while working. The formula is presented as below.

Presenteeism (ability to work affected due to health problems in the past seven days):

$$Percentage\ of\ absenteesim = \frac{Number\ of\ days\ missed\ due\ to\ health\ problems}{Total\ working\ day\ per\ week}$$

$$Percentage\ of\ presenteeism = \frac{affected\ performance\ while\ working\ (VAS)}{10}$$

$$Productivity\ loss\ to\ presenteeism\ (per\ week) = (1 - percentage\ of\ abseteeism) \times percentage\ of\ presenteeism \times daily\ wage$$

For unpaid work, the respondent was asked to evaluate the impact on their work performance and "home-based" daily activities due to health problems in the last seven days by a VAS. While the work performance was regarding presenteeism in paid work, "home-based" daily activities (e.g. walking, dressing, cleaning, collecting firewood, collecting water, cooking etc.) were specified to exclude primary and secondary economic activities. In the VAS, '0' means the health problem had no effect on their work, and '10' means the health problems completely prevented them from working.

As detailed in Chapter 2, two approaches are commonly described to place a monetary value on unpaid work: the opportunity cost approach and the proxy good approach.(5, 182) In the opportunity cost approach, the value placed on lost unpaid work is determined by a person's value of competing time use, such as paid work.(519) With the proxy good approach, the monetary value of unpaid work is based on the value of the closest market

substitute.(5) For example, housework can be valued using the average price of a professional housekeeper. The opportunity cost approach was used to value unpaid work because it was more comparable to paid work in this analysis (using average wages). Similar to presenteeism, the measurement of impact on unpaid work due to health problems is based on the 10-point VAS. Accordingly, productivity loss was multiplied by average wages to value unpaid work.

Unpaid work (ability to perform "home-based" daily activities in the past seven days):

$$Percentage\ of\ activity\ impairment = \frac{activity\ impairment\ (VAS)}{10}$$

$$Indirect\ costs\ due\ to\ unpaid\ work\ (per\ week) = percentage\ of\ activity\ impairment \times\ daily\ wage\ (opportunity\ cost)$$

Lastly, total cost-of-illness was defined as the sum of direct and indirect costs. All costs were extrapolated to a yearly basis and converted to International Dollars in 2020 when necessary.

7.2.5 Statistical Analysis

Descriptive statistics were used in summarising the study variables. Differences in MSK and control groups were assessed applying chi-square and Fisher's exact test as appropriate. A p value of <0.05 was considered statistically significant. For COI analysis, the regression-based approach is commonly used in the literature(106, 184-188) to take into account two important characteristics of the distribution of health care expenditure: the large number of subjects with zero expenditure and the heavily skewed distribution. The various models reported in the literature comprise two-part models designed to take zero expenditure into account. The first part models the individual's decision or ability to

access health care services, i.e., the probability of having health care expenditure different from zero. The second part determines the level of resource utilisation in the subsample of individuals with healthcare expenditures different from zero. The two-part model can be estimated depending on the economic hypothesis adopted to characterise the relationship between the probability of accessing health care and the level of health care consumption. The two-part model is based on the hypothesis that the decision to access health care and the level of health care consumption are not correlated and that these two parts are independent.(404)

Therefore, a two-part model was employed to estimate both direct and indirect costs to account for the excessive number of zero values in each cost item. Furthermore, the level of healthcare consumption in the second modelling part was estimated using a generalised linear model (GLM). Because of the skewness of the cost data, the log-link function with a gamma distribution was chosen in the GLM, rendering the data symmetric to evaluate effects on COI associated with MSK.(85, 403)

Econometric Model covariates

REMS positivity was the independent variable in this econometric model, with “REMS negative” used as the reference group.

Age

MSK disorder is an age-related condition and may have an impact on overall costs as the cohort ages. While costs for health resource utilisation are expected to increase marginally with age, productivity loss due to work loss may differ between age groups in a predominantly agricultural context. Therefore, age was included as a categorical variable, where the youngest group (age less than 50 years) served as the reference group.

Sex

MSK disorder is a disease that is more prevalent in women. It is assumed that costs differ between males and females, in particular those for productivity loss. In this econometric model, female was used as the reference category.

7.2.6 Scenario Analysis

As stated in Section 7.1, households largely bear financial costs as LMICs usually do not offer comprehensive healthcare coverage. In addition to the financial barriers, low disease awareness, underestimation of the effects of symptoms on daily function, work requirements, socioeconomic factors, accessibility to health care and cultural factors may affect the number of people seeking care. Therefore, in addition to estimating the empirical COI due to MSK in the main analysis, this scenario analysis was conducted to explore the uncertainty around the health-seeking behaviour and household OOP expenditures on health to understand the impact from a societal perspective.

Osei et al. found that people with health insurance were 1.284 times more likely to utilise healthcare in rural Ghana.(520) Another systematic review by Okoroh et al. indicated that the uninsured paid 1.4 to 10 times more OOP payments than the insured in Ghana.(521) In other words, the OOP payments were 28.6% to 90% lower for those insured. Therefore, this scenario analysis assumed that people were insured and had reasonable access to health care (at least one visit to the health centre per season). For those who already had visits to the healthcare provider, their visits were multiplied by 1.284. Accordingly, 28.6% and 90% of OOP reduction were adopted to assess the impact of health-seeking behaviour due to health insurance coverage on direct costs, representing low-impact and high impact cases, respectively.

7.2.7 Ethics

The NIHR GHRG- Arthritis study was approved by the Ethics Committee of the Kilimanjaro Christian Medical University College Research Ethics and Review Committee (CRERC) in Moshi, the National Institute of Medical Research Review Committee (NatHREC) of the National Institute Medical Research (NIMR) in Tanzania and the Medical Veterinary and Life Sciences (MVLS) ethics committee at the University of Glasgow, UK. Informed consent was obtained from each patient. For children aged under 18 years, consent from their parents or legal guardian for participation in the research project in addition to assent from the minors who are aged 12-17 years.

7.3 Results

7.3.1 Demographics, Resource Utilisation, and Impact on Productivity

Overall, 159 people with REMS positivity were included in the MSK group, and 467 people with GALS/REMS negativity agreed to participate in the control group. Demographics stratified by the MSK and control group are presented in Table 7.2. People with MSK disorders were older than those in the control group (65.9 vs 60.7, p<0.001). Participants were primarily female in both MSK and control group, with three quarters working in agriculture or manual labour. A higher proportion of participants not working (including unemployment, retired, students or unpaid work) was observed in the MSK group.

Table 7.2 Demographics, stratified by people with and without MSK disorders

	MSK group	**Control group**
Number of participants	159	467
Age years (SD)	65.9*** (14.9)	60.7 (14.9)
Age groups		
<50	13.3%	16.6%
50-59	19.0%	24.2%
60-69	28.5%	33.0%
>70	39.2%	26.1%
Gender		
Male	27.0%	33.0%
Female	73.0%	67.0%
Occupation		
Farmer/manual	75.5%	74.4%
Business/self-employed	5.7%	11.9%
Employed	2.5%	2.4%
Othersφ	16.4%	11.4%

***: p < 0.001; φ: Others including those were unemployed, retired, students, or unpaid house chores.

Health resource utilisation and self-reported expenditures are presented in Table 7.3. A higher proportion of people living with MSK had visited healthcare facilities in the past three months (36.5% vs 17.6%, p<0.01) than those in the control group. For those who

have visited healthcare facilities, pharmacy/dispensary and secondary hospitals were the most frequently visited facilities among the MSK and control groups, respectively. Regarding hospitalisation, no significant differences were found in the frequency and mean length of stay between the MSK and control group. For self-reported expenditure, the average price for each journey to the healthcare facility and household health-related expenditures were comparable between both groups. A large number of people in the control group did not have any health-related expenditure in the past four weeks.

Table 7.3 Health resource utilisation and self-reported expenditures, stratified by MSK and control group

Cost item		MSK	Control
Visit to healthcare facility (3 months)	n	63** (36.5%)	77 (17.6%)
Pharmacy or dispensary	freq	90	45
Health centre$^{\rho}$	freq	19	42
Primary hosital$^{\sigma}$	freq	14	26
Secondary hosital$^{\tau}$	freq	45	88
Tertiary hosital$^{\upsilon}$	freq	15	10
Hospitalisation (12 months)	n	14 (8.8%)	21 (4.5%)
Mean length of hospital stay (SD)		4.4 (4.89)	3.7 (3.58)
Price for each journey to healthcare facility (I$)			
Mean (SD)		6.50 (9.20)	9.30 (12.54)
Median (IQR)		4.50 (1.91-5.63)	5.07 (2.25-10.98)
Household health-related expenditure (4 weeks, I$)			
Mean (SD)		16.13 (30.33)	7.15 (30.45)
Median (IQR)		0.11 (0-11.26)	0 (0-0)

**: $p < 0.01$; ρ : public and private health centre; σ : governmental district hospital; τ : governmental and private specialised hospital, governmental referral hospital; υ : governmental regional hospital; I$: International Dollars; MSK: musculoskeletal

Self-reported outcomes on productivity loss are presented in Table 7.4. People with MSK had fewer working days in the past three months compared to those in the control group (20.4 vs 37.9, p<0.001). Noticeably, 50.3% of participants in the MSK group reported that they had no working days in the past three and therefore resulted in the median of 0. However, working days lost in the last seven days were comparable between the MSK and control group in terms of absenteeism. For presenteeism, although people living with MSK disorders evaluated their work performance as slightly affected by health problems with a mean score of 1.65 (SD: 2.14), the difference was statistically significant compared to the control group. Lastly, the self-evaluated impact on their daily activity due to health problems was similar to work performance among both groups.

Table 7.4 Self-reported outcomes on productivity loss, stratified by MSK and control group

	MSK		Control	
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
Absenteeism				
Working days (3 months)	20.4*** (27.8)	0 (0-38)	37.9 (33.1)	30 (0-72)
Working days lost due to health problems (7 days)	0.23 (0.97)	0 (0-0)	0.09 (0.59)	0 (0-0)
Presenteeism (7 days)				
Impact on work performance (10-point VAS)	1.65*** (2.14)	1 (0-3)	0.70 (1.08)	0 (0-1)
Unpaid work (7 days)				
Impact on daily activity (10-point VAS)	1.65*** (2.14)	1 (0-3)	0.70 (1.08)	0 (0-1)

***: p < 0.001; VAS: visual analogue scale; MSK: musculoskeletal

7.3.2 Regression Outputs

The regression outputs indicated that people with MSK (REMS positivity) were substantially more likely to incur direct costs. People aged 60 years and older were also more likely to incur direct costs compared to the reference group (Table 7.5). For indirect costs, the coefficients indicated that age was the only factor affecting the likelihood of incurring indirect costs as presented in Table 7.6. People who are over 50 years were more likely to incur indirect costs compared to the reference group. On the other hand, the second modelling part for indirect costs indicated that costs conditionally on those with positive costs were substantially higher in the MSK than in the control group

Table 7.5 Regression results: coefficients of the two-part model estimating direct costs

Covariates	**1st modelling part (probability of incurring costs)**			**2nd modelling part (cost ratios conditional on incurring costs)**		
	Coefficient (95%CI)	Std. Err	p value	Coefficient (95%CI)	Std. Err	p value
Age group						
< 50	Reference			Reference		
50 – 59	0.376 (-0.227, 0.980)	0.308	0.221	0.332 (-0.806, 1.471)	0.581	0.568
60 – 69	0.672 (0.110, 1.235)	0.287	<0.05	-0.477 (-1.525, 0.571)	0.535	0.374
> 70	0.871 (0.305, 1.438)	0.289	<0.01	-0.144 (-1.180, 0.892)	0.529	0.786
Gender						
Male	-0.323 (-0.701, 0.056)	0.193	0.09	-0.164 (-0.841, 0.513)	0.345	0.635
Female	Reference			Reference		
Musculoskeletal (MSK) disorder						
MSK	1.282 (0.899, 1.665)	0.196	<0.001	-0.257 (-0.860, 0.346)	0.308	0.405
Control	Reference			Reference		

Table 7.6 Regression results: coefficients of the two-part model estimating indirect costs

Covariates	1st modelling part (probability of incurring costs)			2nd modelling part (cost ratios conditional on incurring costs)		
	Coefficient (95%CI)	Std. Err	p value	Coefficient (95%CI)	Std. Err	p value
Age group						
< 50	Reference			Reference		
50 – 59	1.260 (0.707, 1.812)	0.281	<0.001	0.355 (-0.398, 1.450)	0.383	0.354
60 – 69	0.853 (0.333, 1.373)	0.265	<0.01	0.423 (-0.319, 1.507)	0.376	0.26
>70	0.745 (0.217, 1.273)	0.269	<0.01	0.317 (-0.408, 1.536)	0.382	0.407
Gender						
Male	0.025 (-0.322, 0.372)	0.177	0.886	-0.059 (-0.481, 0.647)	0.220	0.788
Female	Reference			Reference		
Musculoskeletal (MSK) disorder						
MSK	0.246 (-0.125, 0.617)	0.189	0.194	0.794 (0.212, 1.343)	0.228	<0.001
Control	Reference			Reference		

7.3.3 Direct and Indirect Costs

As presented in Table 7.7, the average annualised direct costs for people with MSK were I$154.49 (95%CI 88.15-236.00), which was mainly driven by health-related OOP expenditures (I$122.60, 95% CI 69.6-184.08) and followed by costs for outpatient visits (I$20.73 95%CI 6.21-38.52). A similar distribution of cost components in direct costs was found in the control group. Among cost components, costs for outpatient visits and health-related OOP expenditure incurred by people with MSK were both considerably higher than those in the control group. Noticeably, costs for hospitalisation were comparatively low in both groups.

In contrast, the average annualised indirect costs were estimated at I$176.27 (95%CI 77.70-223.92) in people living with MSK, which were 2.48 times higher than those incurred by people in the control group (I$70.84 95%CI 29.60-91.73). Costs for presenteeism and unpaid work were comparable within both groups. Regarding the distribution of cost components in indirect costs, absenteeism accounted for a higher proportion of indirect costs in the MSK compared to the control group.

Table 7.7 Average annualised cost, stratified by MSK and control group (I$ 2020)

Cost items	MSK (95%CI)	Control (95%CI)
Direct costs	**154.49 (88.15-236.00)**	**94.81 (50.33-143.87)**
Outpatient visit	20.73 (6.21-38.52)	7.29 (1.99-13.63)
Hospitalisation	3.57 (0.90-5.50)	3.12 (0.84-5.09)
Transportation	8.59 (1.55-14.73)	5.61 (1.18-11.52)
Out-of-pocket expenditure	122.60 (69.6-184.08)	78.11 (43.62-119.59)
Indirect costs	**176.27 (77.70-223.92)**	**70.84 (29.60-91.73)**
Absenteeism	73.98 (31.96-118.06)	26.95 (11.12-42.07)
Presenteeism	51.07 (27.52-61.51)	20.32 (10.39-25.78)
Unpaid work	51.97 (23.34-59.22)	22.79 (9.95-27.12)
Total costs	**328.67 (231.81-413.78)**	**163.10 (91.70-218.85)**

7.3.4 Scenario Analysis

The scenario analysis assumed that people were insured and had reasonable access to health care. For those who already had visits to the healthcare provider, their visits were multiplied by 1.284. The lowest and highest OOP reduction from 28.6% to 90% were adopted to assess the impact on direct costs as low-impact and high impact cases, respectively.

In the main analysis, direct costs were predominantly attributable to OOP expenditures, which accounted for 79% of direct costs. As shown in Figure 7.4, outpatient visits and transportation costs increased due to more visits being imputed in the low-impact and high-

impact cases. OOP expenditures still accounted for 63% of direct costs in the low-impact case. However, costs for outpatient visits replaced OOP expenditures as the largest component in direct costs, followed by a substantial decrease in annualised direct costs from I$155.49 to I$64.34.

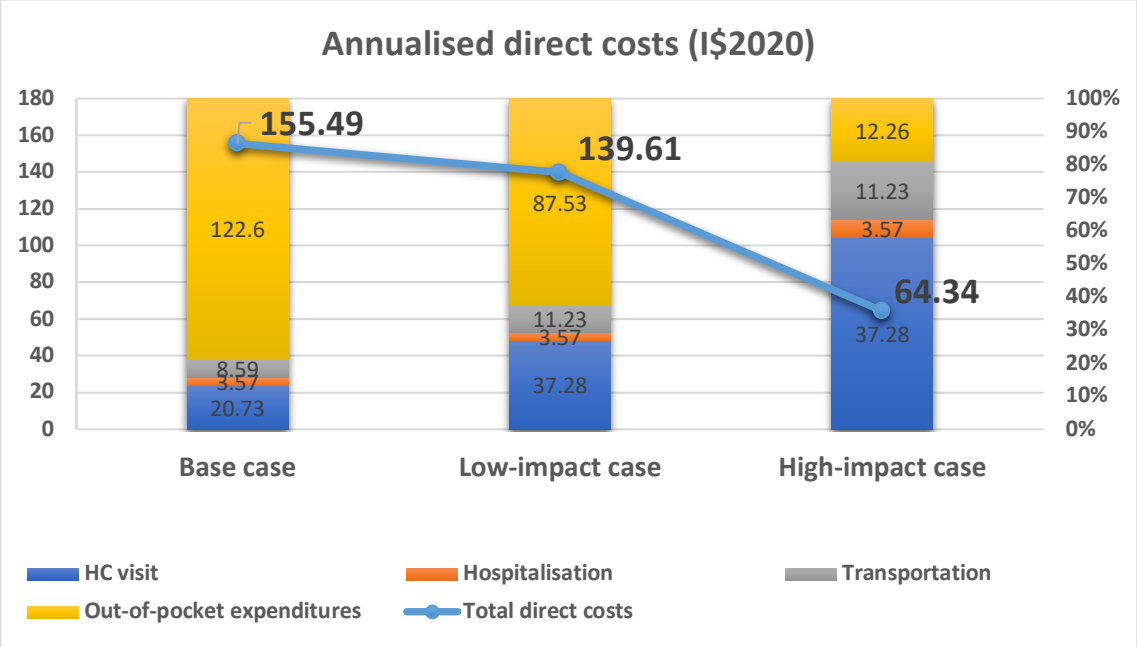


Figure 7.4 Scenario analysis on the impact of health insurance and on direct costs

7.4 Discussion

This chapter presented a COI study due to MSK in Tanzania by using the developed COI questionnaire in the community survey. Given the lack of available data on anticipated costs/categories in this low resource setting, a control group with MSK was included to elucidate the findings. Overall, the results suggested that MSK disorders imposed a considerable financial burden on the household (I$154.55 per year, 95%CI 88.15-236.00) in Tanzania. Total annualised direct and indirect costs incurred by people living with MSK disorders were nearly twice as high as those in the control group. Direct costs were mainly driven by OOP expenditure in both MSK and control group. Compared to the control group, indirect costs accounted for a higher proportion of total costs in people with MSK (53.6% vs 43.4%). McIntyre et al. indicated that indirect costs often can be 2 to 3.6 times than direct costs in LMICs.(442) However, the included studies are historical or focused on infectious diseases,(522-525) as well as different approaches to estimating direct and indirect costs.

Considering that COI studies in MSK disorders are sparse in Africa,(443, 444) the findings are discussed in relation to literature emerging from other LMICs as well. Although the study participants did not have a confirmed diagnosis of RA, this study has moved beyond current evidence on the COI due to RA in LMICs. As discussed in Chapter 6, all the cross-sectional studies used convenience samples at study facilities.(345, 354, 357, 425, 426, 428, 430) The heavy reliance on convenience samples taken from people seeking and obtaining treatment, often at hospitals, will almost certainly result in an upward bias in costs for the average person with the condition.(461) Among the MSK group, only 36.5% of the participants had any visit to healthcare facilities in the preceding three months. Thereby, outpatient attendance and hospitalisation costs were substantially lower than OOP expenditures. In contrast, direct costs were primarily attributable to drug costs or

hospitalisation among other COI studies due to RA in LMICs. As shown in the scenario analysis, when people were insured and had reasonable access to healthcare, outpatient attendance replaced OOP expenditures as the largest share in direct costs, followed by a significant reduction in direct costs from a societal perspective. Despite that not every patient will seek care when perceived ill, health-seeking behaviour is a particularly important methodological challenge faced by researchers conducting a COI study in LMICs to truly reflect the economic burden in patients.(442, 453)

In addition to considering health-seeking behaviour due to the financial barrier or disease awareness, finding appropriate unit costs for healthcare service in LMICs is demanding.(454, 490) Although proxies could be adopted, for example, this study used differentiated unit costs for healthcare services in Tanzania provided by the WHO-CHOICE. The proximal unit costs were estimated by a regression model based on a set of standard assumptions, and thus, estimates can be considered 'average' values of unit costs for public facilities in the country.(518) However, costs for drug and diagnostic tests were not included in both unit costs for outpatient attendance and hospitalisation, albeit these costs were assumed to be covered in OOP payments. The limitation on the comprehensiveness of cost components in the unit costs by WHO-CHOICE may affect the accuracy of cost estimates. Nevertheless, the much broader variation in market prices may not accurately reflect the economic value of resources in LMICs.(445) Adopting these unit costs to estimate COI in the low-resource setting may increase the comparability and generalisability of cost estimates across studies. What's more critical is the transparency in reporting on the estimation of COI. The presentation of cost data should be accompanied by a clear description of how the data were estimated to prevent misuse or misapplication of the data for other purposes.

In the present study, the human capital approach and opportunity cost approach were adopted to estimate paid and unpaid work in indirect costs, respectively. Costs for absenteeism were measured by the workday loss due to health problems in the past seven days. Moreover, as far as is known, this is the first study that attempted to estimate values of presenteeism and unpaid work in COI due to MSK in LMICs. The finding shows that people with MSK incurred nearly 2.5 times higher indirect costs than those in the control group, where absenteeism accounted for the largest share. Noticeably, while nearly three-quarters of study participants reported they worked in agriculture in both MSK and control groups, 50.3% and 25.3% of them answered they had no working days in the past three months, respectively. This might be attributable to seasonal effects on the farm work, and people with MSK were relatively older than controls. For unpaid work, although it has reminded the respondents to consider the impact on their normal 'home-based' daily activities separately from previous questions on absenteeism and presenteeism. Results between presenteeism and unpaid work were very close in both MSK and controls. Similar to the large number of zero working days, this might be due to seasonal effect, age, gender, and the distinction between paid and unpaid work in this context. As highlighted in Chapter 6, it is still uncertain whether the approaches to valuing indirect costs which were developed for a HIC setting are also relevant to a LMIC setting where the labour market operates quite differently, in particular for indirect costs. In this study, the control group of people without MSK provided useful information to interpret the implications. However, this will require more information and further research to address.

In contrast to the other empirical study in Chapter 5 of this thesis, this study used self-reported data to estimate the COI due to MSK as administrative records are currently not suitably robust in many low-income settings. A strength of this study is that it allowed to incorporate more relevant data regarding the estimation of COI in the LMIC setting at its

designing stage. In addition to the methodological challenges on unit costs and valuing indirect costs discussed above, this study faced several methodological limitations. Firstly, specific recall periods were applied to different cost items to ensure all relevant events could be captured and take recall bias into account. Still, the results indicate there is a need to improve or modified the measurement and valuation of indirect costs for the LMIC or agricultural setting. Secondly, it was designed to collect the breakdown of household OOP expenditures on health. Unfortunately, only the sum of monthly health-related expenditures was returned, although it did not affect the estimation of total direct costs. This could be due to the difficulty and infeasibility for participants to answer how they spent OOPs in great detail.

Lastly, our local colleagues reported difficulty finding participants when they visited selected households, particularly during work hours. Although they had rescheduled the interview to weekends whenever possible, this may explain that a higher proportion of females were included in addition to the nature of MSK disorders.

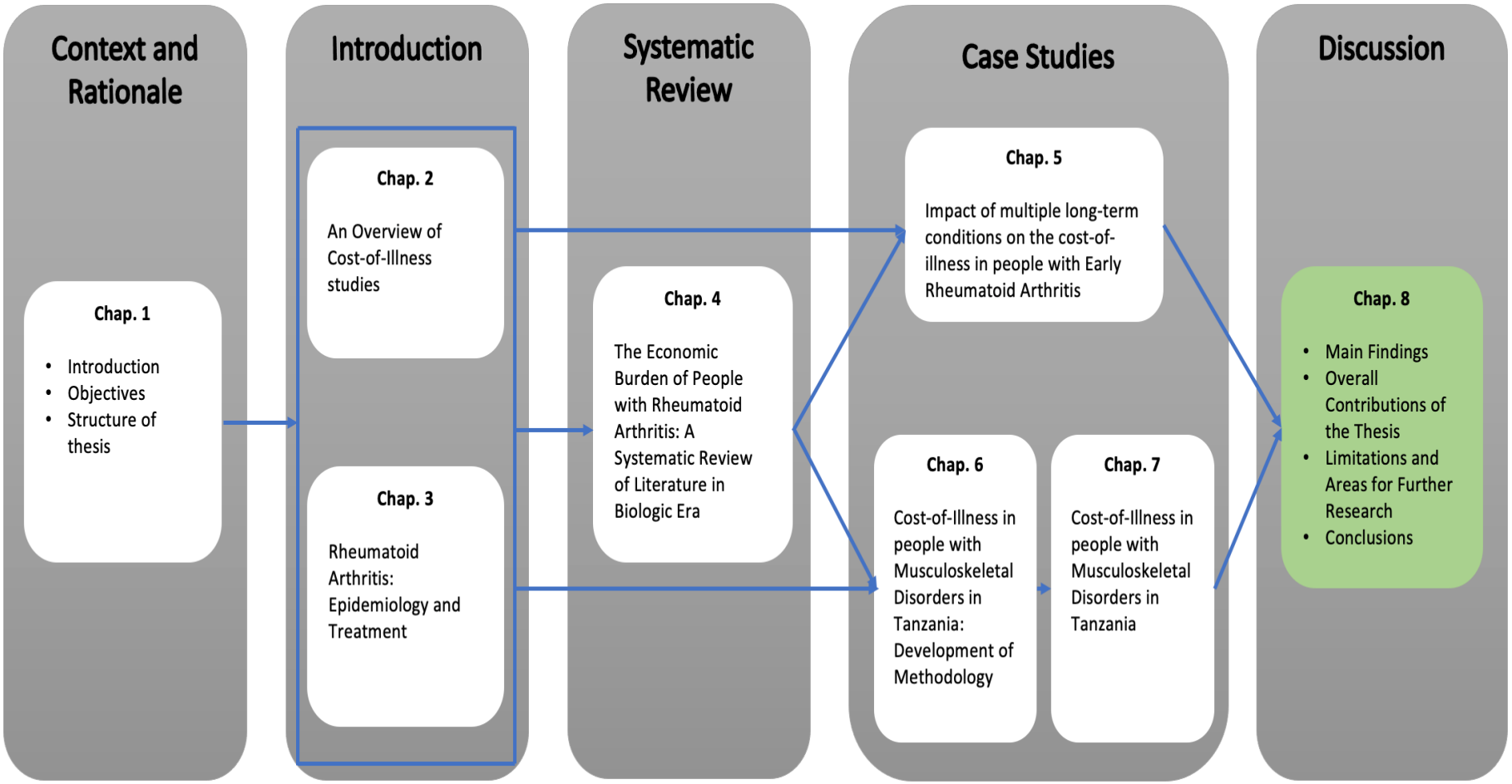
7.5 Chapter Summary

Due to the scarcity of COI studies due to MSK disorders in sub-Saharan Africa, this empirical study contributes to an understanding of information on the COI due to MSK in Tanzania. The findings indicate that MSK disorders imposed a considerable financial burden on the household in Tanzania, primarily attributable to OOP expenditures. Total annualised direct and indirect costs incurred by people living with MSK disorders were nearly twice higher than controls.

This study also highlights several methodological challenges for conducting a COI study in LMICs. Due to the lack of adequate financial protection, health-seeking behaviour is

particularly an important methodological challenge faced by researchers to truly reflect the economic burden in patients. In valuing direct costs, finding appropriate unit costs for healthcare service in LMICs is demanding. In the absence of specific unit costs for the study context, adopting universal unit costs, for example, published by the WHO-CHOICE, may increase the comparability and generalisability of cost estimates across studies. However, the transparency in reporting the estimation of COI is more critical. For indirect costs, it is still uncertain whether the approaches to valuing indirect costs which were developed for a HIC setting are also relevant to a LMIC setting where the labour market operates quite differently. Although this study has attempted to address this beyond absenteeism by modifying validated questionnaires, there is still a need to improve the estimation of indirect costs in LMICs, accounting for seasonal effects, sociocultural factors, and different economic activities. In the absence of validated tools in LMIC setting, a control group of people without the condition provides useful information to interpret the implications.

To achieve the robustness of COI studies under different scenarios, this chapter, together with Chapter 6, discusses the methodological considerations of estimating the COI in LMICs and demonstrates by developing a COI study due to MSK in Tanzania. The next chapter will summarise the findings and contribution of this thesis, and discuss the implications of findings for policymaking and future research.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CHAPTER 8. DISCUSSION

The aim of a cost-of-illness (COI) study is to identify, measure and value all the cost domains of a particular disease, including direct, indirect and intangible costs.(63) Estimates of the COI can inform us how much society is spending on a particular disease and the contribution of relevant cost components. The information provided by COI studies helps develop preventive efforts which may reduce the burden of disease, particularly for chronic diseases that impact heavily on health expenditures and productivity loss for the whole society.(15, 16) Moreover, COI studies can enable comparisons between the burden of different diseases and across years when using the same methodology.(2, 7-10) Comparisons of costs across disease areas are useful to aid decision-makers in prioritising scarce healthcare resources for areas with the highest burden.(11) However, inconsistencies in the designs and methodologies that COI studies are conducted and a lack of transparency in reporting have made interpretation and comparison difficult and have limited the usefulness of results in health decision making.

This thesis set out to improve the estimation of COI, specifically on the case studies of rheumatoid arthritis (RA) in Scotland and musculoskeletal (MSK) disorders in Tanzania. The thesis had four overarching research questions:

1) How has the COI in RA been estimated in the current literature?
    - What are the methodological approaches to estimating the COI in RA?
2) What is the COI of RA in Scotland?
    - How do coexisting long-term conditions impact on the COI in people with early RA?

- What are the methodological challenges in estimating the COI in RA using an inception cohort linked to routinely collected health data?

3) What is the COI in people with musculoskeletal disorders in Tanzania?
    - What are the methodological challenges in estimating the COI in low- and middle-income countries?
4) How could the estimation of COI studies in RA/MSK be improved?

Through the systematic review, the thesis evaluated methods that are currently used in the identification, measurement and valuation in COI studies. To achieve the robustness of COI studies under different scenarios, two case studies were performed to discuss the advantages and challenges of different approaches and contexts to estimating COI. This last chapter summarises the findings of the thesis, its contributions to policy, the limitations inherent in the methods, and areas where further research is needed.

8.1 Main Findings

8.1.1 Methodological Challenges in Estimating the COI in RA

The first research question was addressed in Chapter 4, based on the foundation of Chapter 2 and Chapter 3. In Chapter 4, the systematic review mapped the existing evidence on COI of RA in the biologic era, examining how cost components have been measured and estimated. Seventy-two studies were included from 28 countries, with differences in populations, healthcare systems, cost estimates, and methodologies across and within countries. Most studies conducted retrospective analyses from claim databases or disease registries rather than developing a dedicated primary data collection. In addition, most included studies estimated costs directly and entirely attributed to RA, whereas few studies measured all expenditures incurred to the people with RA or incremental costs by using matched-control or regression-based approaches.

In Chapter 4 of this thesis, the systematic review for COI in RA shows the proportion of drug costs, as the main component contributing to direct costs, was increasing over time since the introduction of biologics, although no statistically significant increase in this trend could be established. However, the statistically significant decrease in the proportion of costs for hospitalisation suggests that costs have shifted to other components of direct costs. For indirect costs, absenteeism and work disability were the most commonly reported components. Work disability, which mainly included pay-outs for disability pensions, was identified as the key cost driver of indirect costs. While absenteeism and work disability are relatively straightforward to measure, presenteeism is still rarely addressed and lacks a clear measurement methodology.(359, 360) Regarding the valuing approach, although human capital approach (HCA) was more commonly used, this approach has been criticised as possibly over-estimating actual indirect costs, while the friction cost approach (FCA) is relatively difficult to implement as it requires detailed information or assumptions.(82) The findings suggested that the HCA was the most commonly used approach when reported, whereas two studies only used the FCA.(331, 332) Among the six studies adopting both approaches,(324, 333-337) the FCA usually served as an alternative approach in the sensitivity analysis.

Chapter 4 also identifies the major methodological challenge: comparability across the COI studies in RA. The inconsistency of methodologies has resulted in a wide variation in cost estimates and the distribution of cost components. For example, drug costs contributed to between 9.8% and 87.2% of direct costs across studies. As outlined in the Chapter 1, the incomparability of cost estimates across studies can frustrate policymakers to find a definitive answer and thus limit its usefulness in health decision making. Vassal and colleagues (2017) published a detailed methodological principle and developed a checklist for costing studies.(483) However, it focused more on programme costing (i.e. strategies,

services and interventions). In the absence of an appropriate quality assessment tool for COI studies, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (319) was modified to evaluate the quality of included studies. The CHEERS checklist is designed to assess good reporting of economic evaluations, so items regarding the choice of model, assumptions, and parameters are optional for few COI studies that use a model-based approach. Items specific to economic evaluation, such as comparator, outcome measurement, and effectiveness, are replaced by population (optional for studies with matched population), cost components, and cost. Overall studies scored well against the 21 criteria of the modified CHEERS checklist. Four items relating to study perspective, characterising uncertainty, characterising heterogeneity, and conflicts of interests scored less with over a quarter of studies failing to report the details.

Different methods lead to different results, and thus limit the generalisability and comparability. As demonstrated in Chapter 4, current COI studies have underestimated the true economic burden of RA due to indirect costs not being taken into consideration routinely. Even when indirect costs were included, the methods varied. As a result, indirect costs accounted for 39.4% to 85.5% of total direct and indirect costs. Moreover, presenteeism in indirect costs varied substantially from 8.8% to 92.9%. In the absence of a comprehensive guideline for COI studies, particularly for indirect costs, transparency in reporting is essential for readers to interpret the results. For example, justification should be given for the cost components included and how they were defined and measured, along with some discussion of the expected effects of important excluded components. Also, sufficient documentation of data sources, assumptions and estimation methods are required, along with an explanation of their main limitations. When this transparency and communication are not present in COI studies, policymakers cannot understand the implications of findings or compare studies to inform policy decisions.

This chapter set the frame for the remaining chapters of the PhD. The remainder of the PhD examines these methodological challenges and other constraints faced by researchers working on COI studies, and identifies opportunities for the research community to take action to improve the comparability and reliability of COI going forward.

8.1.2 Cost-of-illness in people with RA in Scotland

Chapter 5 presents a COI study by implementing one of the most common approaches to estimating COI in the context of RA in Scotland. In addition, it has investigated the impact of coexisting LTCs on the COI in RA by using the two comorbidity measures to categorise distinct LTC burden, including 'RA alone', 'RA plus single LTC', and 'RA plus multiple LTCs (MLTCs)'.

As outlined in Chapter 5, LTC and MLTCs are now an established priority for both research (31) and clinical practice (32, 33) owing to the high prevalence of coexisting diseases among patients. In the context of an ageing population and the life-long nature of RA, the management of MLTCs is particularly relevant in order to provide the best possible outcomes and to minimise unintended complications and costs.(23, 223) To date, existing studies have focused on the added economic burden associated with specific LTCs (368, 369) or groups of selected LTCs in established RA.(370-372) The findings show that among people with early RA, people with MLTCs incurred direct costs that were almost five times higher and indirect costs that were three times higher than in people with RA only. The findings provide additional support for the importance of aggressive screening and early intervention to prevent the progression of MLTCs in people with RA. Both RA and LTC-related outcomes should be considered in formulating evidence-based policies and guidelines for RA management.

As the Charlson Comorbidity Index (CCI) is a generic comorbidity measure, relying on detailed hospital records, the six comorbidities in the European Alliance of Associations for Rheumatology (EULAR) recommendations were adopted as an alternative LTC grouping method. The EULAR grouping method used multiple data sources, including prescribing data, hospital records and cancer registry. Although the monetary values were substantially lower across all categories compared to the CCI grouping, the pattern of direct and indirect costs increased with the LTC category was comparable. Generic measures, such as CCI, are easy to use and compare, but particularly in RA might miss some diseases as only hospitalisations are included, which are typically quite severe. Besides, wide confidence intervals were observed, in particular for those with MLTCs by using CCI. This implies that the level of MLTCs (e.g. severity and number of LTCs) was very heterogeneous. The EULAR grouping method implemented in the sensitivity analysis was useful to categories distinct comorbidity burden. It could serve a desirable framework to consider for future studies, when multiple types of data are available.

As identified in Chapter 4, most COI studies in RA conducted retrospective analyses from claim databases or disease registries rather than developing a dedicated primary data collection. In Chapter 5, a COI was estimated by using a RA inception cohort linked with routinely collected health data. Indirect costs were estimated by the self-reported sick leaves in the previous week and length of inpatient stay from linked health data. From the systematic review presented in Chapter 4, the findings conclude that indirect costs account for 3% to 86% of total costs across studies. In the main analysis of Chapter 5, indirect costs only accounted for 18.1% of total costs. In contrast, 73.6 % of total costs were indirect costs when adopting external sources on sickness from TIRA2, which collected absenteeism using a health economic questionnaire. Apart from data availability, this

indicated the importance of methodology in collecting indirect costs and should be considered early in the designing stage when a societal perspective is desirable.

8.1.3 Cost-of-illness in people with MSK in Tanzania

Chapters 6 and 7 address the third research question of this thesis: what is the COI in people with MSK in Tanzania and what are the methodological challenges to estimate COI in LMICs? In addition to Chapter 2, which discusses the theoretical background of COI studies and the conventional methodologies, the differences and challenges of the identification, measurement, and valuation of COI in LMICs were outlined in Chapter 6. Studies identified in Chapter 4 were then used to inform critiques of existing COI studies in LMICs study. Building on the lessons learned from previous chapters, a context-specific questionnaire that incorporates relevant components regarding the estimation of COI in the LMIC setting was developed.

In Chapter 6, the review found that eight of eleven COI studies in RA that have been conducted in LMICs were based on convenience samples taken from individuals seeking and receiving treatment at hospitals,(345, 354, 357, 372, 425, 426, 428, 430) except for three studies used data from expert opinions,(427) literature review (431) and retrospective analysis from health insurance database.(429) For those cross-sectional studies used convenience samples at study facilities, sample sizes were often arbitrary and vary widely across studies. In terms of methodological rigour, the reliance on convenience samples taken from individuals who are seeking and receiving treatment at hospitals will likely result in an upward bias in costs for the average person with the condition.(461) In the second case study presented in Chapter 7, people with MSK disorders were identified by two screening tools, the Gait Arms Legs Spine (GALS), and Regional Examination of the Musculoskeletal System (REMS) through a tiered approach. The screening tools and tiered

approach were helpful to identify people with MSK, particularly in rural areas, and thus avoid upward bias in costs that captured in a hospital setting. The findings suggested that MSK disorders imposed a considerable financial burden on the household in Tanzania. Although the study population were not RA-confirmatory cases as it requires a blood test, it is expected the effect will be magnified in RA cases.

Chapter 7 presents the results of the COI study due to MSK in Tanzania by using the developed questionnaire. Given the lack of available data on anticipated costs/categories in this low-resource setting, a control group of people without the condition provide useful information to interpret the implications in this study.(157, 461, 504). The results of Chapter 7 are meaningful for the LMIC context, particularly in sub-Saharan Africa. As administrative records are currently not suitably robust in many low-income settings, this study used self-reported data to estimate the COI due to MSK in the community survey. However, it should be noted that self-reported data that were not validated diagnostically may be biased,(526-528) since people may (intentionally or unknowingly) understate some behaviours like smoking or alcohol/drug abuse, overstate physical activity, be unaware of undiagnosed conditions (529) or misunderstand their conditions (e.g. confusing osteoporosis and arthritis).

Financial costs are largely borne by households as LMICs usually do not offer comprehensive healthcare coverage. In addition to financial barriers, low disease awareness, underestimation of the effects of symptoms on daily function, work requirements, socioeconomic factors, accessibility to health care and cultural factors can affect the number of people seeking care. Indeed, only 36.5% of participants with MSK disorders had visited the healthcare provider in the past three months. Purely considering those costs that arise relative to available household resources will not provide a complete

picture of COI. Therefore, the scenario analysis in Chapter 7 explores the impact of health insurance coverage on their health-seeking behaviour and COI. Direct costs were predominantly attributable to OOP expenditures (79%) in the main analysis. In contrast, costs for outpatient visits and transportation costs increased due to more visits being imputed in the low-impact and high-impact cases. Costs for outpatient visits replaced OOP expenditures as the largest component in direct costs, followed by a substantial decrease in annualised direct costs from I$139 to I$65 in the high-impact case. Despite that not every patient will seek care when perceived ill, many of these people are often the most vulnerable, and methods need to be developed to help researchers estimate their costs. In LMICs, health-seeking behaviour is a particularly important methodological challenge faced by researchers conducting a COI study to truly reflect the economic burden in patients.(442, 453)

In addition to considering health-seeking behaviour due to the financial barrier or disease awareness, finding appropriate unit costs for healthcare service in LMICs is challenging.(454, 490) In Chapter 7, proximal unit costs for outpatient attendance and hospitalisation were adopted from the WHO-CHOICE.(518) Costs for drug and diagnostic tests were not included in both unit costs for outpatient attendance and hospitalisation, albeit these costs were assumed to be covered in OOP payments. The limitation on the comprehensiveness of cost components in the unit costs by WHO-CHOICE may affect the accuracy of cost estimates. Nevertheless, the much broader variation in market prices may not accurately reflect the economic value of resources in LMICs.(445) Adopting these unit costs to estimate COI in the low-resource setting may be a trade-off option between the accuracy and comparability of cost estimates across studies. What's more critical is the transparency in reporting on the estimation of COI. The presentation of cost data should be

accompanied by a clear description of how the data were estimated to prevent misuse or misapplication of the data for other purposes.

For indirect costs, while nearly three-quarters of study participants reported they worked in agriculture in both MSK and control groups, 50.3% and 25.3% of them answered they had no working days in the past three months, respectively. This might be attributable to seasonal effects on the farm work, and people with MSK were relatively older than controls. Moreover, results between presenteeism and unpaid work (home-based activities) were very close in both MSK and controls. As highlighted in Chapter 6, it is still uncertain whether the approaches to valuing indirect costs which were developed for a HIC setting are also relevant to a LMIC setting where the labour market operates quite differently. In particular, for indirect costs, a control group of people without the condition could provide useful information to interpret the implications as shown in this study.(157, 504)

8.2 Overall Contributions of the Thesis

This thesis has made a number of contributions to the understanding of the methodological challenges in COI studies. The empirical findings from two case were complementary to each other in terms of different approaches and contexts to estimating COI. It has also made contributions in terms of advancing methods for estimating COI in RA. The contributions of this thesis are described below.

8.2.1 The Economic Burden of People with Rheumatoid Arthritis in Biologic Era

This systematic review has synthesised contemporary literature in COI due to RA. In the face of ageing populations, rising healthcare expenditure, and evolving treatment pathways, it is important to understand not only the health gains but also where costs are being incurred and what cost savings are occurring as a consequence, when making health

policy decisions. The systematic review has concluded that a decreasing trend in inpatient costs chronologically suggested a cost shift in other components of direct costs. Indirect costs still contributed a considerable proportion of total costs, with work disability being the main cost component. Economic analyses that do not incorporate or appropriately measure indirect costs will underestimate the full economic impact of RA.

Although it is difficult to draw a meaningful chronological trajectory to examine the change in landscape, owing to disparities in costing methodologies, perspectives, and healthcare settings across studies, the decreasing trend in costs for hospital expenditure and surgery suggested a cost shift in other components of direct costs. In practice, Louie et al. showed that the rates of joint surgery, a long-term consequence of poorly controlled RA, decreased significantly in the mid-2000s compared to the mid-1980s.(530)

When estimating the COI of RA, it is crucial to consider the impact of absenteeism and presenteeism and informal care from patients' and carers' perspectives. In the context of RA, indirect costs constitute a considerable proportion of the total cost of illness. The evidence is not strong enough to support the argument that biologics live up to their promise that expensive drug costs could easily be recovered. More importantly, a clear understanding of indirect costs can provide an important guide and resource for policy development to support RA patients for continuing to work.

8.2.2 Impact of Multiple Long-Term Conditions on the Cost-of-Illness in People with Early RA

This is the first study to evaluate the economic burden of MLTCs in people with early RA, including direct and indirect costs. While specific LTCs in established RA is known to incur additional healthcare costs, little is known about the impact of MLTCs on the COI in

early RA, particularly for indirect costs. Compared to indirect costs, direct costs increased more substantially with the LTC category. In addition to increased costs with LTC, there appeared to be more effect of increasing age associated with the category of LTC in direct costs.

The findings provide additional support for the importance of active screening of LTCs in people with RA. More importantly, it shows the impact of LTC on the COI that occurs early in the disease, when there may still be an opportunity to intervene and change this. Both RA and MLTCs-related outcomes should be considered in formulating evidence-based policies and guidelines for RA management. It is important that clinicians work closely with the multidisciplinary team in RA as well as provide patients financial advice.

8.2.3 Cost-of-Illness in People with Musculoskeletal Disorders in Tanzania

This is the first study to evaluate the COI in people with MSK disorders in sub-Saharan Africa. Due to the scarcity of COI studies due to MSK disorders in sub-Saharan Africa, this empirical study contributes to an understanding of information on the COI due to MSK in Tanzania. The research in this thesis has confirmed MSK disorders imposed a considerable financial burden on the household in Tanzania, primarily attributable to OOP expenditures. Total annualised direct and indirect costs incurred by people living with MSK disorders were nearly twice higher than controls from a societal perspective.

To date, rheumatology services are limited or non-existent in many parts of sub-Saharan Africa,(531) treatment strategies for RA still focus on pain relief. Although the study participants were not yet RA-confirmatory cases, this study has moved beyond current evidence on the COI due to RA in LMICs. It is expected the effect will be magnified in RA cases. The findings would be helpful for researchers and policymakers to assess the impact

on society at the advent of biologic or biosimilar disease-modifying antirheumatic drugs in this region.

As shown in the scenario analysis, when people were insured and had reasonable access to healthcare, outpatient attendance replaced OOP expenditures as the largest share in direct costs, followed by a significant reduction in direct costs from a societal perspective. This could provide additional support for the pursuit of Universal Health Coverage programme in Africa region.

8.3 Limitations and Areas for Further Research

There are, however, a few limitations noted with this thesis – often due to practical restrictions. In Chapter 4, total costs included various components that were not homogenous across included studies, and a breakdown of total costs into individual components was not always reported. Therefore, it was inappropriate to pool estimates from different countries or perform formal quantitative analyses (meta-analysis). Instead, data were assembled and analysed available narratively and explored the heterogeneity between studies.

In Chapter 5, it was reliant on data that had already been collected in the Scottish Early Rheumatoid Arthritis (SERA) inception cohort. This limited study design has prevented direct comparison of other studies. Indeed, using real-world evidence to address the economic burden of patients with RA is getting popular as it can provide detailed resource data (e.g. drugs, hospitalisation, diagnostic tests), and it is less costly in time and resources than a dedicated primary data collection. However, non-medical costs and indirect costs are less likely to be included. Ideally, future disease registries or clinical trials should invest on incorporating indirect costs, including absenteeism, presenteeism and unpaid

work at the early stage. In particular, validated questionnaires should be considered whenever possible to increase the comparability of results as it would greatly facilitate the estimation of total cost-of-illness in RA.

As discussed in Section 8.1.3, it is still uncertain whether the approaches to valuing indirect costs which were developed for HICs are also relevant to LMIC setting where the labour market operates quite differently. This study has attempted to address this beyond absenteeism by modifying validated questionnaires and indicated that people with MSK incurred almost 2.5 times higher indirect costs than controls. However, there is still a need to improve the estimation of indirect costs in LMICs, accounting for seasonal effects, sociocultural factors, and different economic activities.

Lastly, although not reported in any of the included studies in Chapter 4, the advent of less expensive biosimilars provides the potential for reducing pressure on healthcare budgets. So far, there has been no COI study exploring the economic impact of biosimilars in RA since the first biosimilars for infliximab and etanercept were approved in the US and Europe in 2016. It has been suggested that highly equivalent and lower cost biosimilars could reduce the pressure on healthcare budgets and compensate for inequalities in access to therapy potentially caused by economic differences between countries.(362)] Future studies in RA should focus on the economic impact of informal care from patients' perspective, presenteeism, and the entry of biosimilars.

8.4 Conclusions

This thesis has demonstrated the need for improved estimation of COI studies. Good quality of COI studies is not easy to do. Indirect costs still need more focus to be improved in terms of data collection and costing approaches, particularly in presenteeism and unpaid

work. Future disease registries and clinical trials should consider incorporating the collection of indirect costs by the use of validated instruments. On the other hand, health-seeking behaviour needs to be considered in the estimation of COI, particularly in LMICs. Given that the current methodology in estimating indirect costs may not be feasible in LMICs, a control group without the health condition would be helpful to elucidate the implications. Lastly, health conditions are complex and multi-dimensional, especially when the way we look at them have evolved over time. It is becoming clear that context is also an influencing factor in estimating COI. These complexities need to be taken into account in COI. While many systematic reviews for COI studies have urged the need to increase comparability, it is more crucial to be transparent. COI studies require accurate reporting of context as well as methodological clarity, including the methods used for identifying, measuring, and valuing COI.

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APPENDICES

Appendix A. Search Strategy Using MEDLINE and EMBASE for Cost-of-Illness Studies in Rheumatoid Arthritis

	Query	Results
Search filter for economic studies from Scottish Intercollegiate Guidelines Network (SIGN)		
1	Economics.af.	999167
2	"costs and cost analysis".af.	50521
3	Cost allocation.af.	2844
4	Cost-benefit analysis.af.	175670
5	Cost control.af.	92905
6	Cost savings.af.	92926
7	Cost of illness.af.	52485
8	Cost sharing.af.	11976
9	"deductibles and coinsurance".af.	2107
10	Medical savings accounts.af.	1193
11	Health care costs.af.	118202
12	Direct service costs.af.	1239
13	Drug costs.af.	35774
14	Employer health costs.af.	1159
15	Hospital costs.af.	48982
16	Health expenditures.af.	27664
17	Capital expenditures.af.	2918
18	Value of life.af.	9518
19	Exp economics, hospital.af.	11293
20	Exp economics, medical.af.	10963
21	Economics, nursing.af.	4266
22	Economics, pharmaceutical.af.	3028
23	Exp "fees and charges".af.	9333
24	Exp budgets.af.	61612
25	(low adj cost).af.	181669
26	(high adj cost) .af.	80703
27	(health?care adj cost$).af.	80964
28	(fiscal or funding or financial or finance) .af..	2312342
29	(cost adj estimate$).af.	20117
30	(cost adj variable) .af.	813
31	(unit adj cost$).af.	17841
32	(economic$ or pharmacoeconomic$ or price$ or pricing) .af.	2520189
33	Or/1-32	4692540
33	rheumatoid arthritis.sh.	189714
34	33 and 34	7494
35	limit 35 to yr="2000 - 2019"	6867

	Query	Results
36	Not editorials	6655
37	Not conference paper and abstract	4537
38	Not review	3154
39	Not letter	3031
40	Not animals	2981

Appendix B. CHEERS checklist—modified version for cost-of-illness study*

Section/item	Item No	Modified Recommendation
Title and abstract		
Title	1	Identify the study as a COI study or use more specific terms such as direct costs, indirect costs (productivity loss), and economic burden.
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and data source), results, and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study.
		Present the study question and its relevance for health policy or practice decisions.
Methods		
Target population and subgroups	4	Describe characteristics of the population and subgroups analysed, including why they were chosen.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.
Population (optional)	7	If the target population is compared with a matched population, describe the characteristics and how they have been matched.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
Cost components	9	Describe what cost components are taken into account and their relevance to the perspective of the study.
Estimating resources and costs	10	Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	11	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model (optional)	12	If presented, describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions (optional)	13	If presented, describe all structural or other assumptions underpinning the decision-analytical model.

Section/item	Item No	Modified Recommendation
Analytical methods	14	Describe all analytical methods supporting the COI study. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters (optional)	15	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Cost	16	Report mean values for the main categories of estimated costs, as well as mean difference between the matched groups if been compared.
Characterising uncertainty	17	Describe the uncertainty of the estimated cost (such as confidence interval, standard deviation, and sensitivity analysis), together with the impact of methodological assumptions (such as discount rate, study perspective).
Characterising heterogeneity	18	If applicable, report differences in costs that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
Discussion		
Study findings, limitations, generalisability, and current knowledge	19	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.
Other		
Source of funding	20	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the study. Describe other non-monetary sources of support.
Conflicts of interest	21	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.

* *The CHEERS checklist is designed to assess good reporting of economic evaluations, items regarding to choice of model, assumptions and parameters are kept as optional for few COI studies use model-based approach. Also, items specific to economic evaluation, such as comparator, outcome measurement, and effectiveness are replaced by population (optional for studies with matched population), cost components, and cost.*

Appendix C. Characteristics of included studies, arranged by region, country, and year

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
Europe			
Radner 2014, Austria(336)	N=356 11.5 years, 79.8% female, 59.9 years	Cross-sectional survey, taking into account both direct and indirect costs	RA clinic at a hospital
Westhovens 2005, Belgium(329)	Early, n=48 0.5 years, 65% female, 59.2 years Late, n=85 12.5 years, 79% female, 55.5 years	Cross-sectional survey on early (< 1 year) and late RA patients, taking into account direct costs on societal perspective	A multicentre longitudinal study from private rheumatology practices and university hospitals
Klimes 2014, Czech(331)	N=261 14.5 years, 84.3% female, 56.38 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	At the centre for treatment of rheumatic diseases
Kruntoradova 2014, Czech(332)	N=77 7.4 years, 64.9% female, 45.3 years	Cross-sectional survey, taking into account indirect costs on societal perspective	Three specialised centres for the treatment of rheumatic diseases
Sogaard 2010, Denmark(351)	N=3,704 75% female, 60.6 years	Cross-sectional survey taking into account indirect costs	A cohort of patients from 11 hospital-based rheumatologic clinics
Kobelt 2008, France(341)	N=1,487 18 years, 83.5% female, 62.7 years	Cross-sectional survey, taking into account both direct and indirect costs on payer's and societal perspective	Anonymous mail survey from all members of a national patient association (ANDAR)
Loppenthin 2017, Denmark(532)	N=25,547 72.3% female, 24% 60-69 years	Retrospective database analysis, taking both direct and indirect costs into account on societal perspective	National Patient Registry (NPR)
Flipon 2009, France(346)	N=180, 71.1% female	Cross-sectional survey, taking into account both direct	Survey based on patients in the French Very Early

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
		costs and indirect on payer's perspective	Rheumatoid Arthritis (VErA) cohort
Beresniak 2011, France(321)	NA	Direct costs-modelling of RA according to disease activity categories on payer's perspective	Resource utilisation and unit costs estimated through expert opinion and simulated using distribution ranges for each item
Chevreul 2014, France(323)	N=813 214 days, 76.8% female, 47.6 years	Retrospective database analysis and survey data of patients on distinct DMARDs treatment, taking into account direct costs on payer's perspective	A multicentre, prospective study of patients with early arthritis (ESPOIR Cohort)
Beck 2015, France(348)	N=862, 80.3% female	Retrospective database analysis of patients on biologic treatments, taking into account direct costs on payer's perspective	Administrative claims data from the DCIR and PMSI databases
Fautrel 2016, France(533)	Not reported	Retrospective database analysis, taking into account direct costs on payer's perspective	A national claim database (EGB)
Martikainen 2016, Finland(327)	N=7,831 4 years (median), 71% female, 46 years	Retrospective database analysis, taking into account indirect costs on societal perspective	Health insurance database
Ruof 2003, Germany(344)	N=338 8.4 years, 76% female, 58.4 years	Retrospective database analysis, taking into account both direct and indirect costs on payer's perspective	Health insurance database (AKON) and regional physicians' association (KVN)
Hulsemann 2005, Germany(340)	N=136 77% female, 57.4 years	Cross-sectional survey to determine out-of-pocket expenditures,	A multicentre randomised controlled prospective trial

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
		taking into account direct costs on patients' perspective	
Merkesdal 2005, Germany(337)	N=234 8 years, 76% female, 53 years	Cost data derived from questionnaires of patients matched with payer's database, taking into account indirect costs on societal perspective	A multicentre randomised controlled prospective trial matched with a health insurance database (AKON)
Kirchhoff 2011, Germany(333)	N=180 8.5 years, 69% female, 53 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	A multi-centre clinical trial on RA
Huscher 2015, Germany(334)	N=3,327 10.3 years, 75.8% female, 63.1 years	Retrospective database analysis, taking into account both direct and indirect costs on societal perspective	The National Database of the Collaborative Arthritis Centres (NDB)
Ziegelbauer 2018, Germany(349)	N=678 57.5% female 51.1 years	Retrospective database analysis of patients on TNFi treatment, taking direct costs into account	German statutory health insurance funds database
Horvath Cs 2014, Hungary(534)	N=976, 87% female	Retrospective database analysis in long-term care settings, taking into account direct costs on payer's perspective	The National Health Insurance Fund Administration (NHIFA)
Della Rossa 2010, Italy(358)	N=34 14 years, 67.6% female, 66.5 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	RA patients in Pisa
Verstappen 2007,	<2/ 2-6/ 6-10/ >10 years, n=73/ 214/ 114/ 60	Cross-sectional survey, taking into	A cross-sectional study of the Utrecht Rheumatoid Arthritis

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
Netherlands(328)	0.9/ 4/ 7.7/ 19 years 77%/ 73%/ 62%/ 78% female 54/ 58/ 61/ 60 years	account direct costs on payer's perspective.	Cohort study group (SRU)
Merkesdal 2005, Germany(337)	N=234 8 years, 76% female, 53 years	Cost data derived from questionnaires of patients matched with payer's database, taking into account indirect costs on societal perspective	A multicentre randomised controlled prospective trial matched with a health insurance database (AKON)
Kirchhoff 2011, Germany(333)	N=180 8.5 years, 69% female, 53 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	A multi-centre clinical trial on RA
Huscher 2015, Germany(334)	N=3,327 10.3 years, 75.8% female, 63.1 years	Retrospective database analysis, taking into account both direct and indirect costs on societal perspective	The National Database of the Collaborative Arthritis Centres (NDB)
Ziegelbauer 2018, Germany(349)	N=678 57.5% female 51.1 years	Retrospective database analysis of patients on TNFi treatment, taking direct costs into account	German statutory health insurance funds database
Horvath Cs 2014, Hungary(534)	N=976, 87% female	Retrospective database analysis in long-term care settings, taking into account direct costs on payer's perspective	The National Health Insurance Fund Administration (NHIFA)
Della Rossa 2010, Italy(358)	N=34 14 years, 67.6% female, 66.5 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	RA patients in Pisa
Verstappen 2007,	<2/ 2-6/ 6-10/ >10 years,	Cross-sectional survey, taking into	A cross-sectional study of the Utrecht

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
Netherlands(328)	n=73/ 214/ 114/ 60 0.9/ 4/ 7.7/ 19 years 77%/ 73%/ 62%/ 78% female 54/ 58/ 61/ 60 years	account direct costs on payer's perspective.	Rheumatoid Arthritis Cohort study group (SRU)
Kvamme 2012, Norway(335)	N=1,152 6 years, 72% female, 57 years	Retrospective database analysis of patients on DMARDs or biologic treatments, taking into account both direct and indirect costs on societal perspective	A Norwegian DMARD register (NOR-DMARD). Patients were from five rheumatology departments in hospitals
Malinowski 2016, Poland(350)	N=8,800	Retrospective database analysis, taking into account indirect costs on payer's perspective	The Social Insurance Institution database
Miranda 2012, Portugal(356)	N=351 8.2 years, 84% female, 59 years	Cross-sectional survey, taking into account direct costs on societal perspective	A cohort of RA patients (FRAIL Study)
Leon 2016, Spain(416)	N=1,095, 74% female, 62 years	Retrospective database analysis, taking into account direct costs on payer's perspective	A cohort of RA and spondyloarthritis patients (EMAR-II) study
Jacobsson 2007, Sweden**(343)**	N=613 16.7 years (median), 73.9% female, 66 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	RA patients living in Malmo
Hallert 2014, Sweden(326)	N=125 6 years, 67% female, 55 years	Cross-sectional survey on patients after 6 years follow-up of early RA, taking into account both direct and indirect costs on societal perspective	A longitudinal prospective multicentre TIRA study
Eriksson 2015, Sweden(324)	Prevalent, n=49,829	Retrospective database analysis,	The Swedish National Patient Register and

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
	9.7 years, 73% female, 65.1 years Incident, n=2,695 69% female, 61.9 years	taking into account both direct and indirect costs on societal perspective	the Swedish Rheumatology Quality Register.
Johansson 2015, Sweden(535)	Moderate, n=1,638 10 years, 74% female, 56 years High, n=1,870 10 years, 75% female, 60 years	Retrospective database analysis of patients grouped into moderate and high disease activity by DAS28, taking into account direct costs	The Swedish Rheumatology Quality Register, primarily on early arthritis and patients on biologic treatments
Hallert 2016, Sweden(325)	N=340 70.3% female, 59 years	Cross-sectional survey on early RA patients, taking into account both direct and indirect costs on societal perspective	A longitudinal prospective multicentre study (TIRA2)
Malhan 2010, Turkey(431)	N=562	Literature review of patients on DMARDs or TNFi treatment, taking into account direct costs on payer's perspective	Patient data taken from a reference article; cost data collected from hospital bills, social security institution price lists, and Ministry of Health drug price list.
Malhan 2012, Turkey(427)	NA	Expert opinions, taking into account both direct and indirect costs on societal perspective	A panel of experts chosen from 20 clinics at tertiary healthcare institutions nationwide
Baser 2013, Turkey(429)	Prevalent, n=1,920 83.5% female, 53.9 years old Incident, n=693 80% female, 52.1 years	Retrospective database analysis of patients grouped into prevalent and incident cases, taking into account direct costs on payer's perspective	Turkish national health insurance database (MEDULA)
North America			

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
Fautrel 2007, Canada(347)	N=121 79.3% female, 63% between 40-64 years	Cross-sectional survey on patients and general population, taking into account both direct and indirect costs on societal perspective	Patients recruited from their treating physicians; general population enrolled from random digit dialling for people living in Quebec
Barnabe 2013, Canada(417)	N=1,086 13.6 years, 72.1% female, 55.1 years	Retrospective database analysis of patients on biologic treatments, taking into account direct costs on societal perspective	The Alberta Biologics Pharmacosurveillance Program (ABioPharm) linked with provincial health care administrative database
Tarride 2013, Canada(185)	N=233 75.5% female, 58.9 years	Cross-sectional survey on patients linked retrospective database analysis, taking into account direct costs	Canadian Community Health Survey (CCHS) linked to the Ontario Health Insurance Program (OHIP)
Thanh 2013, Canada(536)	N=1,222 13 years, 69% female, 52 years	Retrospective database analysis of patients on DMARDs or TNFi treatment, taking into account indirect costs on societal perspective	The Alberta Biologics Registry
Ohinmaa 2014, Canada(418)	N=1,086 13.6 years, 72.1% female, 55.1 years	Retrospective database analysis of patients on biologic treatments, taking into account direct costs on societal perspective	The Alberta Biologics Pharmacosurveillance Program (ABioPharm) linked with provincial health care administrative database
Yelin 2007, USA(339)	N=4,801	Retrospective database analysis, taking into account direct costs	A national probability sample of households (MEPS)
Kessler 2008, USA(105)	N=333 72.4% female, 52.9% 45–59 years	Cross-sectional survey, taking into account direct costs on	Samples from manufacturing firm (MF) employees and

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
		employer's perspective	commercially insured subscribers
Joyce 2009, USA(368)	RA/+CVD/+depression/+both above n=8,916/608/716/58 77%/55%/88%/81% female, 50.9/58.7/49.6/53 years	Retrospective database analysis of RA patients with co-morbidities, taking into account direct costs on payer's perspective	The PharMetrics Patient-Centric Database
Birnbaum 2010, USA(537)	Privately insured/ Medicare/ Medicaid n=14,317/ 12,157/ 6,415 33.3/ 42.9/ 38.5 months, 70.4%/ 70.6%/ 76.6% female, 49.8/ 70.7/ 45.3 years	Retrospective database analysis, taking into account both direct and indirect costs on societal, employer, patients' and payer's perspectives	Indirect costs from Ingenix Employer Database; direct costs from the Medicare 5% Standard Analytic and Florida Medicaid claims databases
Bonafede 2012, USA(322)	N=26,911 71.7% female, 59.7 years	Retrospective database analysis, taking into account direct costs on societal perspective	The MarketScan Commercial Claims and Encounters (Commercial) Database and the Medicare Supplemental and Coordination of Benefits (COB) Database
Kawatkar 2012, USA(538)	N=5.8 million 61.1% female, 19.3% 45–54 years	Retrospective database analysis, taking into account direct costs on payer's perspective	A national probability sample of households (MEPS)
Simons 2012, USA(539)	N=34,145 80.4% female, 50.6% 40–64 years	Retrospective database analysis, taking into account both direct and indirect costs	A national probability sample of households (MEPS)

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
Kleinman 2013, USA(106)	N=2,705 61.4% female, 45.1 years	Retrospective database analysis, taking into account both direct and indirect costs on employer's perspective	US employees' administrative health care and payroll data in an employer-sponsored health insurance plan
Gunnarsson 2015, USA(184)	N=90,046 76.3% female, 38.8% 45–54 years	Retrospective database analysis, taking into account indirect costs	A national probability sample of households (MEPS)
Zhou 2016, USA(186)	Switched to another TNFi, N=1,169 81.3% female, 49.3 years	Retrospective database analysis of patients on different strategies of TNFi treatment, taking into account direct costs	A US employer-based insurance claims database.
Curtis 2017, USA(540)	N=4,593 11.8 years, 74.4% female, 70.6 years	Retrospective database analysis, taking into account direct costs	A disease registry across 40 states (Corrona) linked to administrative data from Medicare
Grabner 2017, USA(541)	TNFi treatment responders, n=2,337 70.8% female, 52.3 years	Retrospective database analysis of patients on different strategies of TNFi treatment, taking into account direct costs on payer's perspective	Members of 14 large U.S. commercial health plans represented in the HealthCore Integrated Research Database
Chen 2018, USA(542)	N= 115,867 79.4% female, 75.2 years	Retrospective database analysis, taking into account direct costs	Medicare fee-for-service (FFS) claims database
Strand 2018, USA(543)	N= 2527 71.1% female, 56.9 years	Retrospective database analysis of patients on biologic treatments, taking both direct and indirect costs into account	OptumHealth Care Solutions database
Asia			

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
Aggarwal 2006, India(428)	N=101 8.1 years, 89% female, 43.2 years	Cross-sectional survey, taking into account direct costs	RA clinic at a tertiary care hospital
Xu 2014, China(345)	N=829 9.2 years, 78.6% female, 53.3 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	RA clinics at 21 tertiary care hospitals
Hu 2018, China(426)	N=133 68% female, 60.4 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	RA clinics at 2 referral hospitals
Sruamsiri 2018, Japan**(352)**	N=250 9.8 years, 59% female, 52.1 years	Cross-sectional survey, taking into account indirect costs	A nationwide online survey of RA patients
Sruamsiri 2018, Japan(352)	N= 6,153 77% female, 59.2 years	Retrospective database analysis, taking into account direct costs	Hospital claims data from Medical Data Vision Co., Ltd. (MDV)
Lee 2007, Hong Kong(330)	N=147 12.6 years, 76.9% female, 54.7 years	Retrospective database analysis, taking into account direct costs on payer's perspective	RA clinic at a general hospital
Zhu 2011, Hong Kong(355)	N=144 10.8 years ,73% female, 49 years	Cross-sectional survey linked to retrospective database, taking into account both direct and indirect costs on societal perspective	RA clinic at a general hospital
Tanaka 2010, Japan(544)	N=6,823 11.4 years, 83.3% female, 58.4 years	Retrospective database analysis, taking into account direct costs on societal perspective	A disease registry database (IORRA) from RA clinic at Tokyo Women's Medical University
Tanaka 2013, Japan(545)	N=5,265 12.9 years, 83.9% female, 59.5 years	Cross-sectional survey linked to retrospective database analysis, taking into account	A disease registry database (IORRA) from RA clinic at Tokyo Women's Medical University

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
		direct costs on societal perspective	
Kwon 2012, South Korea(546)	N=151,472 77.2% female, 53.1 years	Retrospective database analysis, taking into account direct costs on societal perspective	The national claims database
Lang 2016, Taiwan(547)	Prevalent, n=30,013 Female: male ratio 3.8 Incident, n=2,714 Female: male ratio 3.1	Retrospective database analysis, taking into account direct costs	The National Health Insurance Research Database (NHIRD)
Wang 2016, Taiwan(548)	N=41,269 78.1% female, 59.4 years	Retrospective database analysis for direct costs and a cross-sectional survey for indirect costs	The National Health Insurance Research Database (NHIRD) and 140 patients identified at RA clinics in four hospitals.
Shi 2018, Taiwan(549)	N=110, 645 84% female, 55.5 years	Retrospective database analysis, taking into account direct costs	The National Health Insurance Research Database (NHIRD)
Osiri 2007, Thailand(357)	N=158 10.3 years, 95.6% female, 53.2 years	Cross-sectional survey, taking into account both direct and indirect costs on societal perspective	RA clinic in a major tertiary care facility
Osiri 2013, Thailand(372)	N=684 6.3 years (DMARDs treatment), 90.8% female, 55.2 years	Retrospective database analysis of patients on DMARDs treatment, taking into account direct costs on societal perspective	RA clinic in a major tertiary care facility
Latin America & Australasia			
Chermont 2008, Brazil(430)	N=100 11 years, 92% female, 51 years	Cross-sectional survey linked to retrospective database analysis, taking into account	RA clinic in a tertiary reference centre.

Study reference (Author, Year, Country)	Study population (mean duration of disease, gender, mean age)	Study design	Data source
		direct costs on societal perspective	
De Azevedo 2008, Brazil(425)	N=192 9.79 years, 85.9% female, 47.37 years	Cross-sectional survey, taking into account indirect costs on societal perspective	RA clinic in a tertiary reference centre.
Alvarez-Hernandez 2012, Mexico(354)	N=320 17 months, 89.3% female, 42.7 years	Cross-sectional survey, taking into account both direct and indirect costs on patients' perspective	11 institutional and private centres in five major cities
Cross 2006, Australia(550)	N=70 25.9 years, 84.3% female, 62.7 years	Cross-sectional survey, taking into account direct costs	The Arthritis Cost and Outcome Project, patients were recruited from public and private outpatient clinics

Abbreviations: RA, rheumatoid arthritis; DAS28, Disease Activity Score-28; WPAI, Work Productivity and Activity Impairment questionnaire; WTP, willingness to pay; DMARDs, disease modified anti-rheumatic drugs; TNFi, tumour necrosis inhibitor; CVD, cardiovascular disease; USA, United States of America

Appendix D: Regression results for the EULAR grouping in the sensitivity analysis: coefficients of the GLM model estimating direct costs

Covariates	Coefficient (95%CI)	Std. Err	p Value
Sex			
Male	Reference		
Female	-0.133 (-0.317, 0.052)	0.094	<0.05
Age group			
< 45	Reference		
45 – 54	0.236 (-0.073, 0.546)	0.158	0.135
55 – 64	0.270 (-0.030, 0.569)	0.153	0.007
65 – 75	0.415 (0.107, 0.723)	0.157	<0.01
> 75	0.855 (0.505, 1.206)	0.179	<0.001
SIMD			
1 (most deprived)	Reference		
2	-0.485 (-0.750, -0.220)	0.135	<0.001
3	-0.608 (-0.886, -0.301)	0.142	<0.001
4	-0.389 (-0.656, -0.123)	0.136	<0.01
5 (least deprived)	-0.308 (-0.599, -0.016)	0.149	<0.05
Clinical outcomes			
HAQ-DI score	0.201 (0.051, 0.350)	0.076	<0.01
EQ5D score	-0.080 (-0.599, 0.439)	0.265	0.763
Follow-up period			
Index year	Reference		
2	0.363 (0.074, 0.654)	0.148	<0.05
3	0.538 (0.246, 0.830)	0.149	<0.001
4	0.568 (0.274, 0.861)	0.150	<0.001
5	0.316 (0.019, 0.612)	0.151	<0.05
6	0.471 (0.171, 0.772)	0.153	<0.01
LTC group			
RA alone	Reference		
RA + Single LTC	0.644 (0.402, 0.887)	0.141	<0.001
RA + MLTCs	1.530 (1.307, 1.754)	0.134	<0.001

Abbreviations: EQ5D= EuroQol- 5 Dimension, EULAR: European Alliance of Associations for Rheumatology, GLM= generalised linear model, HAQ-DI= Health Assessment Questionnaire-Disability Index, LTC= long-term conditions, MLTCs= multiple long-term conditions, RA= rheumatoid arthritis, SIMD: Scottish Index of Multiple Deprivation

Appendix E: Regression results for the EULAR grouping in the sensitivity analysis: coefficients of the two-part model estimating indirect costs

Covariates	1st modelling part (probability of incurring costs)			2nd modelling part (conditional on incurring costs)		
	Coefficient (95%CI)	Std. Err	p value	Coefficient (95%CI)	Std. Err	p value
Age group						
18 – 34	Reference			Reference		
35 – 44	-0.142 (-0.441, 0.156)	0.152	0.350	0.100 (-0.112, 0.312)	0.108	0.356
45 – 54	-0.264 (-0.551, 0.024)	0.147	0.072	0.185 (-0.017, 0.386)	0.103	0.073
Sex						
Male	Reference			Reference		
Female	0.137 (-0.097, 0.372)	0.120	0.251	-0.427 (-0.595, -0.258)	0.086	<0.001
SIMD						
1 (most deprived)	Reference			Reference		
2	0.101 (-0.216, 0.420)	0.162	0.531	0.003 (-0.200, 0.205)	0.103	0.978
3	-0.407 (-0.742, -0.071)	0.171	<0.05	-0.016 (-0.258, 0.226)	0.123	0.895
4	-0.443 (-0.762, -0.123)	0.163	<0.01	-0.170 (-0.390, -0.050)	0.112	0.130
5 (least deprived)	-0.317 (-0.673, 0.039)	0.182	0.081	-0.121 (-0.373, 0.130)	0.128	0.344
Clinical outcomes						
HAQ-DI score	0.409 (0.223, 0.596)	0.095	<0.001	0.179 (0.054, 0.305)	0.064	<0.01
EQ5D score	-1.230 (-1.865, -0.596)	0.323	<0.001	-0.024 (-0.452, 0.403)	0.218	0.910
LTC group (using EULAR comorbidity list)						
RA alone	Reference			Reference		
RA + Single LTC	0.752 (0.479, 1.025)	0.139	<0.001	0.167 (-0.041, 0.376)	0.106	0.116
RA + MLTCs	1.064 (0.801, 1.327)	0.134	<0.001	0.495 (0.302, 0.688)	0.098	<0.001

Abbreviations: EQ5D= EuroQol- 5 Dimension, EULAR: European Alliance of Associations for Rheumatology, HAQ-DI= Health Assessment Questionnaire-Disability Index, LTC= long-term conditions, MLTCs= multiple long-term conditions, RA= rheumatoid arthritis, SIMD: Scottish Index of Multiple Deprivation

Appendix F: Cost-of-illness Questionnaire in the NIHR- GHRG study

(Cost-of-illness: Section 1-2; Living standards: Section 3-5)

In general, who would you say has the final decision regarding the household finances (i.e. sale of livestock/ livestock products; seeking medical treatment for people; sending children to school etc.)?

Head	☐
Spouse	☐
Adult son only	☐
Adult men together	☐
Adult women together	☐
Husband/son and wife/mother equally	☐
Other (please specify)	☐
Don't know	☐
Not applicable	☐

Is the household member 18 years or above?

YES	☐
NO	☐

SECTION 1: LABOUR ***(answered by identified individual)***

In the last **12 months**, did you work as an unpaid apprentice OR employee for a wage, salary, commission or any payment in kind; including doing paid apprenticeship, domestic work or paid farm work even if for one hour?

YES	☐
NO	☐

In the last **12 months**, did you run a non-farm business of any size for themselves or the household or help in any kind of non-farm business run by this household, even if for one hour?

YES	☐
NO	☐

In the last **12 months**, did you work on household agricultural activities (including farming, raising livestock, poultry or fishing, whether for sale or for household food) even if just for one hour?

YES	☐
NO	☐

If the answer to at least one of questions 2, 3 and 4 is NO please skip questions 5-13 and go to questions 14-15.

In what type of economic activities did you spend most of your time in the last 3 months?

Please indicate the type for the two activities where you spend most of the time:

Primary economic activity	
Secondary economic activity	

A PAID EMPLOYEE

SELF EMPLOYED WITH EMPLOYEES (NON-AGRIC)

SELF EMPLOYED WITHOUT EMPLOYEES (NON-AGRIC)

UNPAID FAMILY HELPER (NON-AGRIC)

UNPAID FAMILY HELPER (AGRIC)

ON YOUR OWN FARM OR SHAMBA

UNPAID APPRENTICESHIP

If the answer to question 5 is (a) or (g) (wage jobs or apprenticeship), please reply to question 6; otherwise go to question 7.

Do you receive wages, salary or other payments either in cash or in other forms

from this employer for this work?

YES
NO
What kind of work do you usually do in this economic activity?

Describe the occupation and main tasks or duties in at least 2 words:

_____

Please indicate the code for this (TASCO)

_____

What kind of trade or business is it connected with?

Describe the kind of business in at least 2 words:

_____

Please indicate the code for this (ISIC) _____

From question 9 to 12, please refer to the primary and secondary economic activity you indicated in question 5.

During the last 3 months, for how many days did you work in this job?

Primary economic activity	No. days
Secondary economic activity	No. days

During the last 3 months, for how many days per week did you usually work in this job?

Primary economic activity	No. days
Secondary economic activity	No. days

During the last 7 days, did you miss any days from work or feel your ability to work affected in this job because of your health problems?

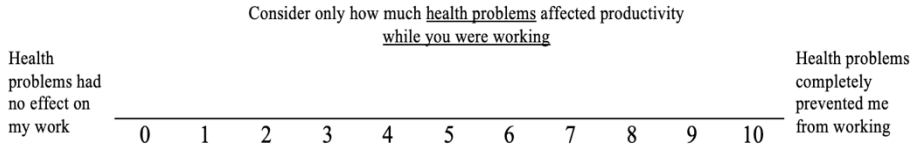
YES, please answer sub-questions b and c.

NO, please go to question 12.

During the last 7 days, how many days did you miss from work in this job because of your health problems?

Primary economic activity	No. days
Secondary economic activity	No. days

In your opinion, during the past 7 days, how much did your health problems affect your ability to work while you were working?



In your opinion, during the past seven days, how much did your health problems affect your ability to perform your normal “home-based” daily activities (e.g. walking, dressing, cleaning, collecting firewood, collecting water, cooking etc.),

excluding the primary and secondary economic activities (already covered in question 5)?

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job

Health problems had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — Health problems completely prevented me from doing my daily activities

SECTION 2 HEALTH (answered by identified individual)

Is this person answering for himself/ herself?

YES ☐
NO ☐

If the answer is NO please respond to the following questions considering the person [person] on whose behalf you are responding.

Have you /[person] visited a health care provider in the past 3 months?

YES, please answer question 22. ☐
NO, please go to question 24. ☐

During the past 3 months, what type of health provider did you /[person] visit and how was the treatment financed?

	Number of times during past 3 months	Covered by: (please choose the most used/relevant option) FREE TREATMENT HEALTH INSURANCE OWN CASH HAD TO WORK FOR PROVIDER USE OF ASSET TOOK LOAN GOT ASSISTANCE DIFFERED BY PROVIDER OTHER, SPECIFY
GOV. PARASTATAL		
REFERRAL/SPEC. HOSP		
REGIONAL HOSPITAL		
DISTRICT HOSPITAL		
HEALTH CENTER		
DISPENSARY		

VILLAGE HEALTH POST		
RELIGIOUS/VOLUNTARY		
REFERRAL/SPEC. HOSP		
DISTRICT HOSPITAL		
HEALTH CENTER		
DISPENSARY		
PRIVATE		
SPECIALISED HOSP		
HEALTH CENTER		
DISPENSARY		
OTHER		
PHARMACY		
NGO		
OTHER, SPECIFY_____		

During the past 12 months, have you visited a hospital (e.g. health facility/centre, district of regional hospital)?

YES, please answer the following sub-questions a-e. ☐
NO, please go to question 26. ☐

How far is the hospital from here? Write answer in kilometres. If less than 1km, write "<1 km"

Distance_____

How did you /[person] usually travel to the hospital (e.g. health facility/centre, district of regional hospital)?

Walk
Bicycle
Motorcycle
Private car
Public taxi/bus
Boat
Donkey/Horse
Other (specify)

How long did the journey take to go from your home to the hospital (e.g. health facility/centre, district of regional hospital) in a round trip?

Hours	
Mins	
Days	

Did you pay for the journey to the hospital (e.g. health facility/centre, district of regional hospital)? If yes, how much in total did you/[person] pay for yourself/himself/herself in a round trip?

YES, Shillings_____ ☐
NO ☐

During the past 12 months, were you/[person] hospitalised or did you/[person] have an overnight stay(s) in a medical facility?

YES, please answer the following sub-questions f-h. ☐
NO, please go to question 26. ☐

During the past 12 months, how many admissions to the hospital did you/[person] have?

Number of admissions	

Adding up all your admissions, please tell us how many nights in total you/[person] were hospitalised in the past 12 months.

Total no. nights	

During the past 12 months, what type of illness or injury did you/[person] have that led to his/her hospitalisation(s)? *Please select all applied.*

FEVER
MALARIA
JOINT PAIN
BROKEN BONE
STOMACH
DIARRHEA
HEADACHE
HEART
LUNG
MATERNITY
OTHER, SPECIFY _____

What are the total costs of your/[person] hospitalisation(s) or admission(s) in a medical facility? *Include estimated values of any in-kind payments.*

Shillings_____

During the last 12 months, did you/[person] visit a traditional healer's or faith dwelling?

YES, please answer the sub-question a. ☐
NO, please go to question 27. ☐

What was the total costs of your/[person] visit(s) at the traditional healer or faith dwelling? *Include estimated values of any in-kind payments.*

Shillings_____

How much in total did the household spend on you/[person] in the past 4 weeks for all illnesses and injuries. Including for prescription medicines, tests, consultation and inpatient fees, if any? *Include estimated values of any in-kind payments.*

Item	Shillings
Prescription medicines	
Consultation	
Inpatient fees	
Tests	
Non-prescription medicines	
Auxiliaries	
Other, specify_____	
Total costs (matched the above)	

SECTION 3: INCOME (answered by nominator on behalf of household)

Which are the two main household main sources of cash income? Please tick the relevant box.

Category	Source 1	Source 2
Sale of food crops		
Sale of livestock		
Sale of livestock products		
Sale of cash crops		
Business income		
Wages or salaries in cash		
Other casual cash earnings		
Cash remittances		
Fishing		
Other (specify)		

What is the total household wage income per month on average from labour, including wage, salary, and excluding livestock or crops?

Please indicate the amount (continuous variable)

Shillings _____

Please indicate the category

1-25,000	☐
25,000-100,000	☐
100,000-200,000	☐
200,000-400,000	☐
400,000-700,000	☐
700,000-1,000,000	☐
Over 1 million	☐
Does not want to answer	☐
Does not know	☐

Please reply to questions 15 and 16 only if the reply to question 5 is b, c, f (the respondent reports being self-employed or owning his own farm)

What gross income did you get from your business/farm in the last month?

Please indicate the amount (continuous variable)

Shillings _____

Please indicate the category

1-25,000	☐
25,000-100,000	☐
100,000-200,000	☐
200,000-400,000	☐
400,000-700,000	☐
700,000-1,000,000	☐
Over 1 million	☐
Does not want to answer	☐
Does not know	☐

What net income did you get from your enterprise/farm in the last month?

Please indicate the amount (continuous variable)

Shillings _____

Please indicate the category

1-25,000	☐
25,000-100,000	☐
100,000-200,000	☐
200,000-400,000	☐
400,000-700,000	☐
700,000-1,000,000	☐
Over 1 million	☐
Does not want to answer	☐
Does not know	☐

Just thinking about your current financial circumstances, would you describe yourself as:

Very rich	☐
Rich	☐
Comfortable	☐
Can manage to get by	☐
Never have quite enough	☐
Poor	☐
Destitute	☐

Just thinking about your financial circumstances that you were living two years ago, would you describe yourself then as:

Very rich	☐

Rich	
Comfortable	
Can manage to get by	
Never have quite enough	
Poor	
Destitute	

SECTION 4: WEALTH (answered by financial respondent)

Please indicate whether you own any of the items in the list below, and how many items your household own? If none, write '0'.

Item	Own item (YES /NO)	No.
Telephone(landline)		
Telephone(mobile)		
Refrigerator or freezer		
Sewing Machine		
Television		
Video / DVD		
Chairs		
Sofas		
Tables		
Watches		
Beds		
Cupboards, chest-of-drawers, boxes, wardrobes, bookcases		
Lanterns		
Computer		
Cooking pots, Cups, other kitchen utensils		
Mosquito net		
Iron (Charcoal or electric)		
Electric/gas stove		
Other stove		
Water-heater		
Record/cassette player, tape recorder		
Complete music system		
Books (not school books)		
Motor Vehicles		
Motorcycle		
Bicycle		
Carts		
Animal-drawn cart		
Boat/canoe		
Wheel barrow		
Outboard engine		
House(s)		
Fan/Air conditioner		
Dish antena/decoder		

hoes		
Spraying machine		
Water pumping set		
reapers		
tractor		
Trailer for tractors		
plough		
harrow		
Milking machine		
Harvesting and threshing machine		
Hand milling machine		
Coffee pulping machine		
Fertilizer distributor		
Power tiller		

Do members of this household own land?

YES	
NO	

If the answer to question 29 is ‘Yes’, go to question 30

How much land do members of this household own in total (in acres)?

Acres _____

How many animals does your household own (at this household and also kept elsewhere)? If none, write ‘0’.

Item description	**No.**
cattle	
Sheep	
goats	
chickens	
donkeys	
pigs	
birds	
cats	
dogs	
other (please specify)	

Over the past 12 months, did you or anyone else in this household borrow from someone outside the household or from an institution receiving either cash, goods or services?

(Include loans for agriculture. Probe for goods or services received on credit.

YES	☐
NO	☐

If the answer to question 30 is 'yes', please reply to questions 31 and 32

How much was borrowed or what was the value of the credit?

Shillings_____

What did you use this loan/credit for? (tick relevant boxes)

Subsistence needs	☐
Medical costs	☐
School fees	☐
Ceremony/wedding	☐
Purchase land	☐
Purchase agricultural inputs	☐
Other business inputs	☐
Purchase agricultural machinery	☐
Buy/build dwelling	☐
Other (specify _____	☐
No reason	☐

SECTION 5 OTHER (answered by nominator on behalf of household)

Over the past two years, have you experienced one of these events? (tick all relevant boxes)

Drought or floods	☐
Crop disease or crop pest	☐
Livestock died or were stolen	☐
Household business failure, non-agricultural	☐
Loss of salaried employment or non-payment of salary	☐
Large fall in sale prices for crops	☐
Large rise in price of food	☐
Large rise in agricultural input prices	☐
Severe water shortage	☐
Loss of land	☐
Chronic/severe illness or accident of household member	☐
Death of a member of household	☐

Death of other family member	☐
Break-up of the household	☐
Hijacking/Robbery/burglary/assault	☐
Dwelling damaged, destroyed	☐
Other (please specify)	☐

Please consider the events you had indicated in question 35, and rank them in terms of severity:

1: _____

2: _____

3:_____

Did the event cause a reduction in household income and/or wealth?

	1 Event	2 Event	3 Event
Income loss			
Wealth loss			
Loss of both			
neither			

<u>If the reply to question 29 is YES please reply to questions 38 and 39</u>

Is the land your household own enough to grow food to feed all the members of your household?

YES	☐
NO	☐

Did your household grow enough food to feed all your household during the last farming season?

YES	☐
NO	☐

How many meals did this household take yesterday?

one	☐
two	☐
three	☐
four	☐
Don’t know/don’t remember	☐

In the past 12 month, how many days did your household not have enough food to eat?

No. days _____

Do you think that this household is able to obtain enough food to eat for the next three or four months?

YES ☐
NO ☐

Appendix G: Regression results for low-impact case in the sensitivity analysis: coefficients of the two-part model estimating direct costs

Covariates	1st modelling part (probability of incurring costs)			2nd modelling part (cost ratios conditional on incurring costs)		
	Coefficient (95%CI)	Std. Err	p value	Coefficient (95%CI)	Std. Err	p value
Age group						
< 50	Reference			Reference		
50 – 59	0.316 (-0.399, 1.031)	0.365	0.386	0.596 (-0.300, 1.493)	0.457	0.194
60 – 69	0.577 (-0.089, 1.242)	0.340	0.090	-0.154 (-0.983, 0.674)	0.423	0.716
> 70	0.949 (0.270, 1.628)	0.346	<0.01	0.231 (-0.577, 1.039)	0.412	0.576
Gender						
Male	-0.498 (-0.954, -0.042)	0.233	<0.05	-0.146 (-0.706, 0.415)	0.286	0.612
Female	Reference			Reference		
Musculoskeletal (MSK) disorder						
MSK	19.469 (979.51, 1018.45)	509.69	0.969	-0.678 (-1.174, 0.182)	0.253	<0.01
Control	Reference			Reference		

Appendix H: Regression results for high-impact case in the sensitivity analysis: coefficients of the two-part model estimating direct costs

Covariates	1st modelling part (probability of incurring costs)			2nd modelling part (cost ratios conditional on incurring costs)		
	Coefficient (95%CI)	Std. Err	p value	Coefficient (95%CI)	Std. Err	p value
Age group						
< 50	Reference			Reference		
50 – 59	0.316 (-0.399, 1.031)	0.365	0.386	0.649 (0.011, 1.287)	0.326	<0.05
60 – 69	0.577 (-0.089, 1.242)	0.340	0.090	0.193 (-0.397, 0.783)	0.301	0.522
> 70	0.949 (0.270, 1.628)	0.346	<0.01	0.391 (-0.184, 0.966)	0.294	0.184
Gender						
Male	-0.498 (-0.954, -0.042)	0.233	<0.05	-0.276 (-0.675, 0.124)	0.204	0.177
Female	Reference			Reference		
Musculoskeletal (MSK) disorder						
MSK	19.469 (979.51, 1018.45)	509.69	0.969	-0.397 (-0.750, -0.044)	0.180	<0.05
Control	Reference			Reference		

Appendix I: Average annualised direct costs: low-impact and high-impact cases in the sensitivity analysis (I$ 2020)

Cost items	Low-impact (95%CI)	High-impact (95%CI)
Direct costs	**138.81 (87.86-215.23)**	**64.85 (37.06-93.40)**
Outpatient visit	37.28 (21.29-57.66)	37.28 (21.29-57.66)
Hospitalisation	3.57 (0.90-5.50)	3.57 (0.90-5.50)
Transportation	11.23 (2.00-19.22)	11.23 (2.00-19.22)
Out-of-pocket expenditure	87.53 (49.70-131.43)	12.26 (6.96-18.41)